THE ACTION OF PHENYLLITHIUM ON SOME DISUBSTITUTED CYANAMIDES

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11/91

THE ACTION OF PHENYLLITHIUM ON SOME DISUBSTITUTED CYANAMIDES

A Thesis

by

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Submitted in partial fulfillment of the
requirements for the degree of
Master of Science

September, 1970

Memorial University
of Newfoundland

This thesis has been examined and approved by:

ACKNOWLEDGEMENTS

The author wishes to express his sincere thanks to Dr. H. J. Anderson for his encouragement and valuable advice throughout the course of this work. Financial assistance from the National Research Council and a demonstratorship from the Department of Chemistry, Memorial University of Newfoundland are gratefully acknowledged.

ABSTRACT

The reactions between phenyllithium and N,N-dimethylcyanamide, N-cyanopyrrolidine (N,N-tetramethylene-cyanamide), N-methyl-N-cyanoaniline (N-methyl-N-phenylcyanamide) and N,N-diphenylcyanamide have been investigated.

2,4-Bis(dimethylamino)-6-phenyl-1,3,5-triazine is obtained from the reaction of one part of phenyllithium and two parts of dimethylcyanamide. Isolation of the intermediates, N,N-dimethylbenzamidine and 1-{α-(dimethylamino)-benzylidene}-3,3-dimethylguanidine was successful. When the ratio is 1:4, besides 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine, 2,4,6-tris(dimethylamino)-1,3,5-triazine is also obtained.

The reactions between phenyllithium and N-cyanopyrrolidine at various ratio are similar to those between phenyllithium and dimethylcyanamide under the same conditions.

The reaction between N-methyl-N-cyanoaniline and phenyllithium yields benzonitrile and 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine. The intermediate, 1,3-dimethyl-1,3-diphenylguanidine, was isolated and the mechanism of the reaction has also been suggested.

Benzonitrile in low yield is the sole product of the reaction between phenyllithium and diphenylcyanamide.

The spectra of the new compounds are also given.

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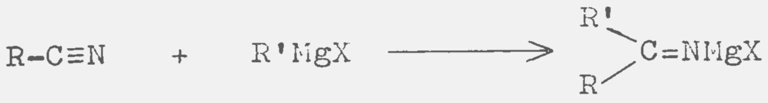
INTRODUCTION

The action of organometallic compounds on nitrile groups has been studied extensively. The reactions between Grignard reagents and nitriles were first studied by Blaise (1). One of the common reactions between Grignard reagents and nitriles is the addition reaction in which one mole of the Grignard reagent is added to one mole of the nitriles to form compounds of the general formula (I). Hydrolysis of (I) gives the corresponding imine and further hydrolysis of the imine yields the corresponding ketone.

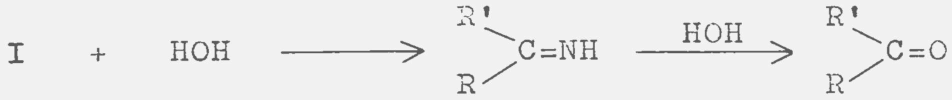
Moderately good yields of substituted amidines were obtained by the interaction between alkyl or aryl cyanides and diethylaminomagnesium bromide, benzylaminomagnesium bromide, methylanilinomagnesium bromide or anilinomagnesium bromide in ethereal solution (2). The amidines are formed by hydrolysis of the complexes of the general formula (II), produced by the addition of the aminomagnesium bromides to the alkyl or aryl cyanides. Benzonitrile and aminomagnesium iodide gives only a small yield of benzamidine and no amidine can be obtained from diphenylaminomagnesium bromide and benzonitrile or p-cyanophenyl methyl sulphone even in anisole at 100^0.

Other reactions between Grignard reagents and nitriles have also been reported (3) when the nitrile is a cyanamide type. For example, good yields of amidine hydrochlorides

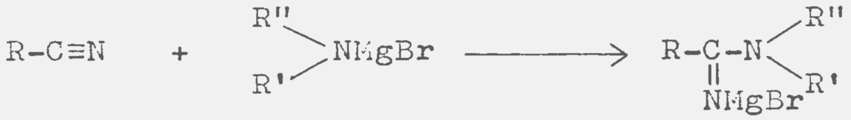


$$\mathrm{R{-}C{\equiv}N} \quad + \quad \mathrm{R'MgX} \longrightarrow \begin{matrix}\mathrm{R'}\\ \mathrm{R}\end{matrix}\!\!>\mathrm{C{=}NMgX}$$

I

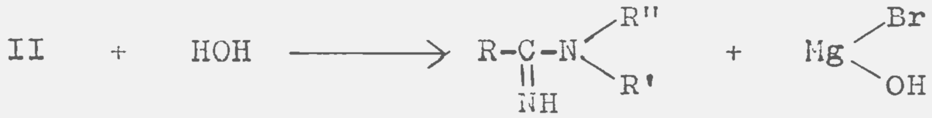


$$\mathrm{I} \quad + \quad \mathrm{HOH} \longrightarrow \begin{matrix}\mathrm{R'}\\ \mathrm{R}\end{matrix}\!\!>\mathrm{C{=}NH} \xrightarrow{\mathrm{HOH}} \begin{matrix}\mathrm{R'}\\ \mathrm{R}\end{matrix}\!\!>\mathrm{C{=}O}$$



$$\mathrm{R{-}C{\equiv}N} \quad + \quad \begin{matrix}\mathrm{R''}\\ \mathrm{R'}\end{matrix}\!\!>\mathrm{NMgBr} \longrightarrow \underset{\mathrm{NMgBr}}{\underset{\|}{\mathrm{R{-}C}}}\mathrm{{-}N}\!<\!\begin{matrix}\mathrm{R''}\\ \mathrm{R'}\end{matrix}$$

II

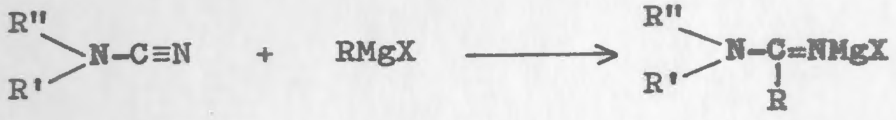


$$\mathrm{II} \quad + \quad \mathrm{HOH} \longrightarrow \underset{\mathrm{NH}}{\underset{\|}{\mathrm{R{-}C}}}\mathrm{{-}N}\!<\!\begin{matrix}\mathrm{R''}\\ \mathrm{R'}\end{matrix} \quad + \quad \mathrm{Mg}\!<\!\begin{matrix}\mathrm{Br}\\ \mathrm{OH}\end{matrix}$$

were reported by Adams and Beebe (4) as resulting from the treatment of dibenzylcyanamide with ethyl-, phenyl-, and p-tolylmagnesium bromide. An amidine was also obtained from dimethylcyanamide and phenylmagnesium bromide, but benzylmagnesium chloride yielded very little amidine together with dimethylamine, toluene, and phenylmalononitrile (5). It was thought that the complexes of the general formula (II) were the intermediates formed by the addition of one mole of the Grignard reagent to one mole of the cyanamides. Hydrolysis of (II) then gave the corresponding amidines.

A moderately good yield of 1,1,3,3-tetraethylguanidine (IV) was obtained from the reaction between diethylcyanamide and diethylaminomagnesium bromide (2) in ethereal solution. The intermediate (III) is formed by the addition of one mole of diethylcyanamide and one mole of diethylaminomagnesium bromide. Hydrolysis of (III) yields (IV).

If the nitrile contains any α-hydrogen, then, another series of reactions may be initiated by the reaction of the Grignard reagent with the α-hydrogen of the nitrile to form compounds of the general formula (V) which may condense with an unchanged nitrile molecule to form the metallic derivative of a β-iminonitriles (VI) which gives (VII) on hydrolysis. This is generally called the Thorpe reaction. Under more drastic conditions there may be formed cyclic trimers of the pyrimidine and pyridine types, (VIII) and (IX), respectively. Trimer (VIII, R = C_6H_5) has been



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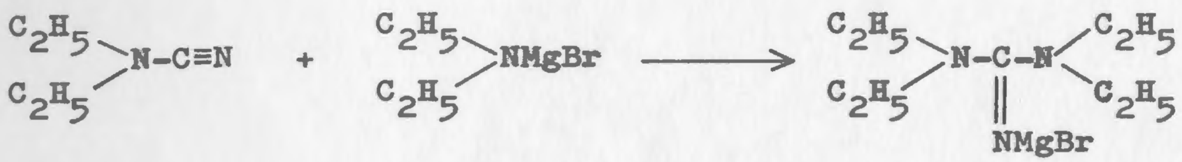
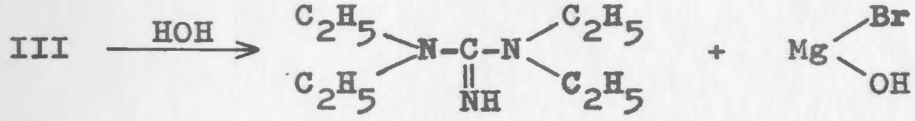
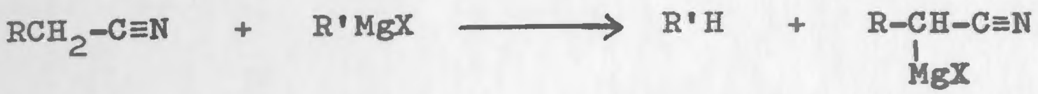


III



IV



$$RCH_2\text{-}C\equiv N \quad + \quad R'MgX \longrightarrow R'H \quad + \quad R\text{-}\underset{\displaystyle MgX}{\underset{|}{CH}}\text{-}C\equiv N$$

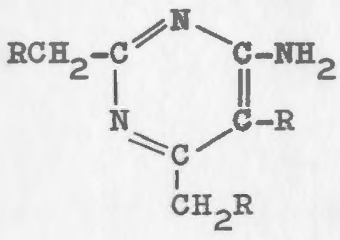
V

$$V \quad + \quad RCH_2\text{-}C\equiv N \longrightarrow RCH_2\text{-}\underset{\displaystyle NMgX}{\underset{\|}{C}}\text{-}\overset{\displaystyle R}{\overset{|}{CH}}\text{-}C\equiv N$$

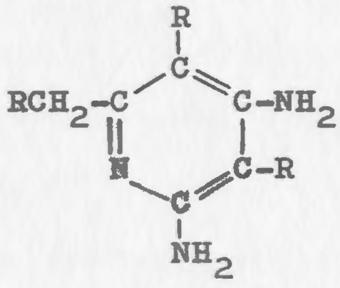
VI

$$VI \quad + \quad HOH \longrightarrow RCH_2\text{-}\underset{\displaystyle NH}{\underset{\|}{C}}\text{-}\overset{\displaystyle R}{\overset{|}{CH}}\text{-}C\equiv N \quad + \quad Mg\begin{matrix}X\\OH\end{matrix}$$

VII



VIII

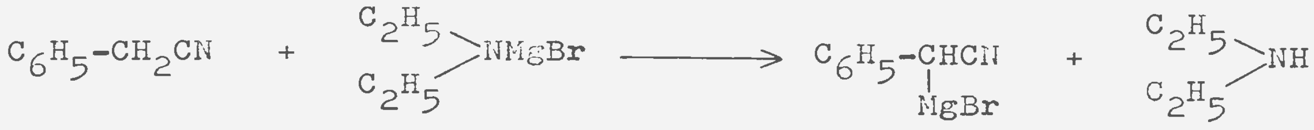


IX

isolated in 35% yield from the reaction mixture of phenylacetonitrile and phenylmagnesium bromide, and trimer (IX, R = CH_3) in 10% yield from propionitrile and ethylmagnesium bromide (6). If metallic sodium is used instead of the Grignard reagent on the nitriles containing α-hydrogen, compounds of the general formula (VII), (VIII) and (IX) are also obtained (7). The other example is the reaction between benzyl cyanide and diethylaminomagnesium bromide (2), in which the Grignard reagent reacts with the α-hydrogen of the benzyl cyanide to form (X) which condenses with another mole of unchanged benzyl cyanide to yield (XI). Hydrolysis of (XI) gives 2-imino-1-cyano-1,3-diphenylpropane (XII). This is analogous to the formation of VII.

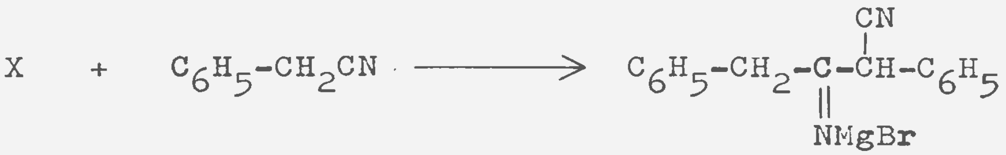
The action of methyllithium on dimethylcyanamide gave a metal-hydrogen exchange reaction (8), in which the dimethylcyanamide reacted as a protic acid towards methyllithium to give methane and a colourless product, (XIII), which reformed dimethylcyanamide when a fresh sample was treated cautiously with methanol.

Sometimes displacement reactions also occur in the reactions between organometallic compounds and nitrile groups. Lettré, Jungmann and Salfeld (9) found that the reaction of phenylmagnesium bromide with N-methyl-N-cyanoaniline was one of the methods which produced benzonitrile. They suggested that the benzonitrile was obtained from the compound, (XIV), which is very similar to (II). The ability to form nitriles



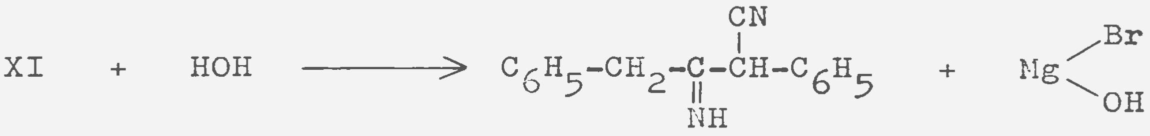
$$C_6H_5\text{-}CH_2CN + \begin{array}{l}C_2H_5\diagdown\\ C_2H_5\diagup\end{array}\!NMgBr \longrightarrow C_6H_5\text{-}\underset{MgBr}{\underset{|}{C}}HCN + \begin{array}{l}C_2H_5\diagdown\\ C_2H_5\diagup\end{array}\!NH$$

X



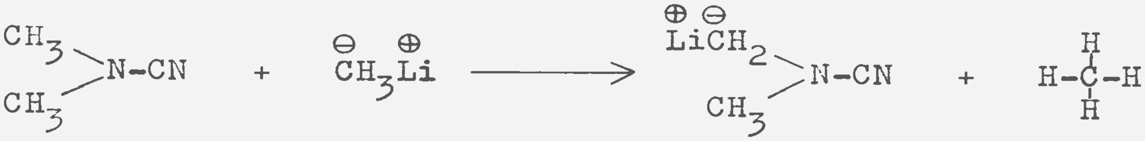
$$X + C_6H_5\text{-}CH_2CN \longrightarrow C_6H_5\text{-}CH_2\text{-}\underset{NMgBr}{\underset{\|}{C}}\text{-}\overset{CN}{\overset{|}{C}}H\text{-}C_6H_5$$

XI



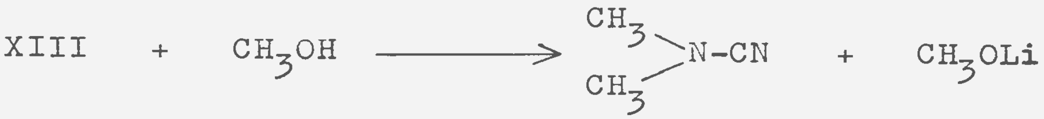
$$XI + HOH \longrightarrow C_6H_5\text{-}CH_2\text{-}\underset{NH}{\underset{\|}{C}}\text{-}\overset{CN}{\overset{|}{C}}H\text{-}C_6H_5 + Mg\!\begin{array}{l}\diagup Br\\ \diagdown OH\end{array}$$

XII

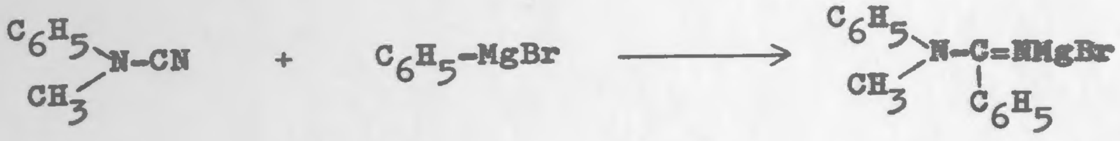


$$\begin{array}{l}CH_3\diagdown\\ CH_3\diagup\end{array}\!N\text{-}CN + \overset{\ominus}{C}H_3\overset{\oplus}{Li} \longrightarrow \begin{array}{l}\overset{\oplus}{Li}\overset{\ominus}{C}H_2\diagdown\\ \quad CH_3\diagup\end{array}\!N\text{-}CN + H\text{-}\underset{H}{\overset{H}{C}}\text{-}H$$

XIII

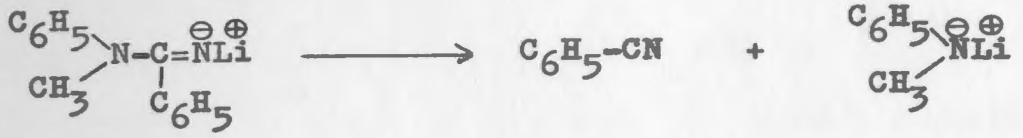


$$XIII + CH_3OH \longrightarrow \begin{array}{l}CH_3\diagdown\\ CH_3\diagup\end{array}\!N\text{-}CN + CH_3OLi$$

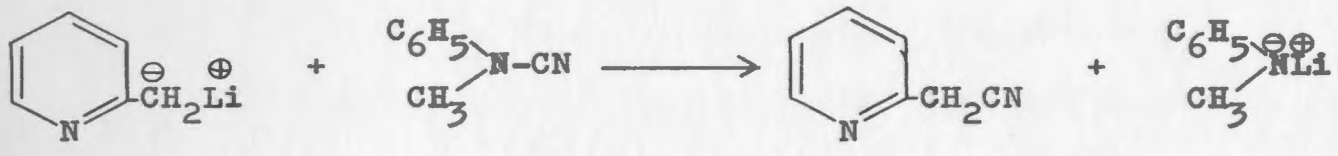


XIV

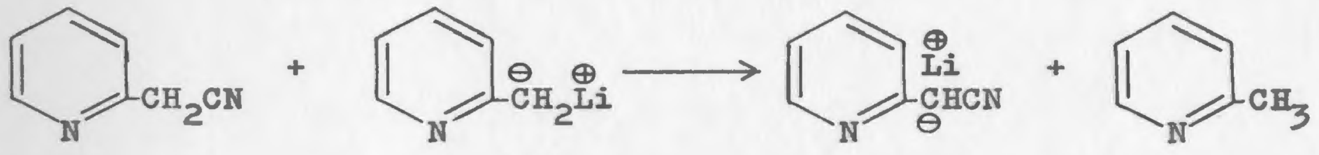
XIV



XV

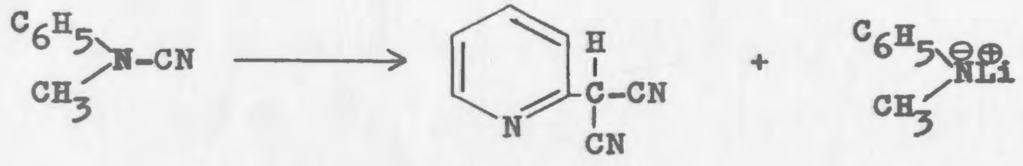


XVI



XVII

XVII

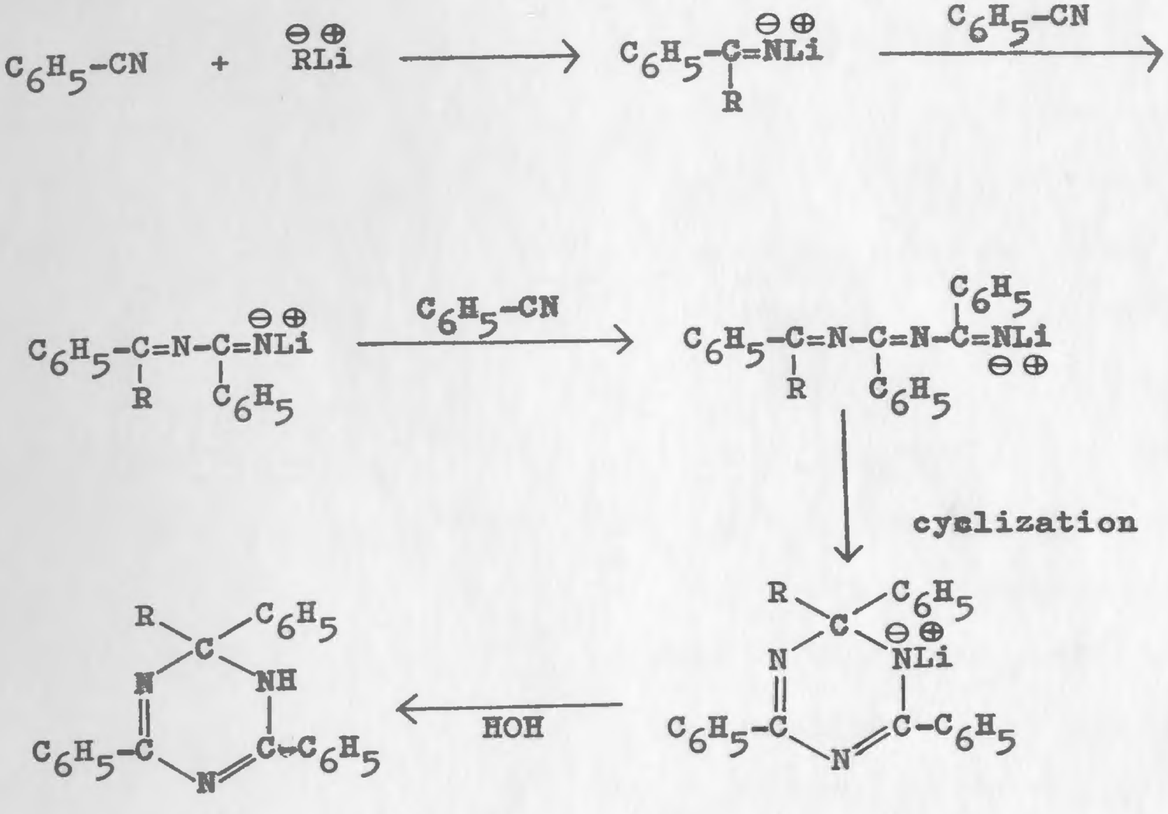


XVIII

from (XIV) is dependent upon the nature of the substituents on the disubstituted cyanamides as well as the organic radical of the Grignard reagent. Benzonitrile can also be obtained from the reaction between N-methyl-N-cyanoaniline and phenyllithium. The intermediate was thought to be (XV) which yields benzonitrile by splitting out one mole of lithium methylphenylamide.

Sometimes dinitriles are also obtained in these types of reactions. For example, 2-pyridylmalononitrile (XVIII) is obtained from N-methyl-N-cyanoaniline and 2-picolyllithium. The first step of the reaction is the formation of 2-pyridylacetonitrile (XVI). Then a hydrogen atom of the methylene group of the 2-pyridylacetonitrile exchanges with the lithium of another 2-picolyllithium. This lithium derivative of 2-pyridylacetonitrile (XVII) then reacts with another mole of N-methyl-N-cyanoaniline to give (XVIII).

In some cases, cyclization takes place in the reactions between organometallic compounds and benzonitrile. R. M. Anker and A. H. Cook (10) found that treatment of methyl-, ethyl-, propyl-, isopropyl-, butyl-, and phenyllithium with benzonitrile all gave dihydrotriazines (XIX) with the additional formation of a little benzophenone from benzonitrile and more phenyllithium. These were the only compounds found. The mechanism of these reactions was formulated as the formation of ketimines with subsequent addition of one or two moles of nitrile as shown by the equations. If phenylsodium was used



XIX

(a) R = $-CH_3$

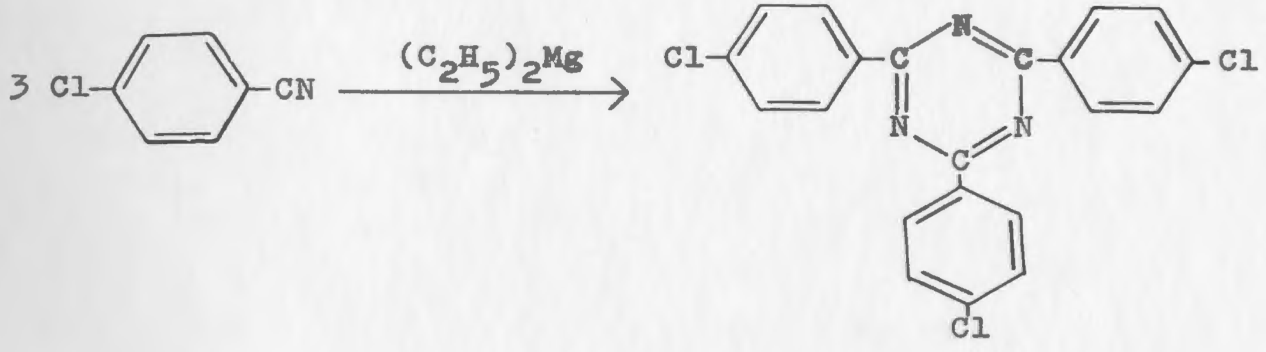
(b) R = $-CH_2CH_3$

(c) R = $-CH_2CH_2CH_3$

(d) R = $-CH(CH_3)_2$

(e) R = $-CH_2CH_2CH_2CH_3$

(f) R = $-C_6H_5$



XX

instead of phenyllithium, the corresponding dihydrotriazine and benzophenone were also obtained. J. C. Citron and E. I. Becker (11) also claimed that 2,4,6-tris(p-chlorophenyl)-1,3,5-triazine (XX) was obtained from the reaction between p-chlorobenzonitrile and diethylmagnesium if the ratio of the former to the latter exceeded 2:1, otherwise only the corresponding imine (I, R = $-C_2H_5$, R' = $-C_6H_4$-p-Cl) was obtained.

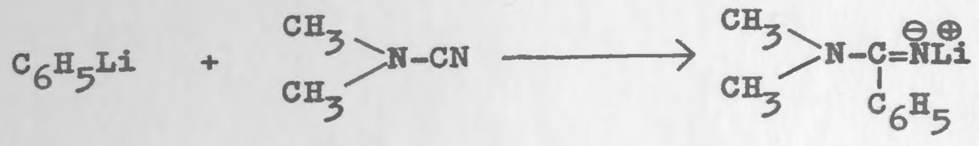
From the examples we have given, it is easy to make the following conclusion. All the above reactions are following similar pathways and the products of the reactions depend on the nature of the organometallic compounds, the substituent groups on both reactants, and the reaction conditions. We also note that there has been no systematic study of the action of phenyllithium and the disubstituted cyanamides, which we will discuss in the following part of this thesis.

DISCUSSION

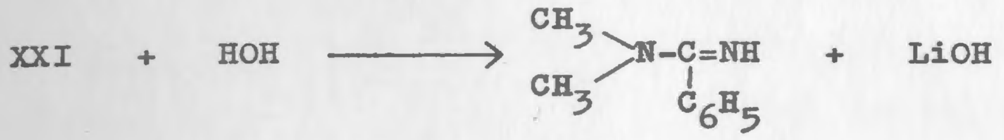
The Action of Phenyllithium on Dimethylcyanamide

We have pointed out in the introduction that in searching the methods of preparation of nitriles, Lettré was able to obtain benzonitriles from the reaction between N-methyl-N-cyanoaniline and phenyl- or substituted phenyllithium. Since dimethylcyanamide was available on the market, if benzonitrile could be obtained by the reaction between this cyanamide and phenyllithium, this meant that benzonitrile could be obtained by a simpler way. In the following part of this section we will discuss the action of phenyllithium on dimethylcyanamide.

When one part of dimethylcyanamide was added to two parts of phenyllithium at room temperature a vigorous reaction took place immediately in the ethereal solution. After the reaction had subsided the lithium salts of organic compounds were hydrolyzed by addition of cold water and the two layers were separated. Both layers presented the characteristic smell of dimethylamine. Instead of benzonitrile, a colourless thick liquid, N,N-dimethylbenzamidine (XXII), was obtained in 38% yield from the ethereal layer at 76-8^0 at 1 mm. pressure. The authentic compound was also prepared from the reaction between phenylmagnesium bromide and dimethylcyanamide in ether solution (5). The mechanisms of these two reactions should be very similar to each other. The lithium salt of N,N-dimethylbenzamidine (XXI) is formed by the addition of one

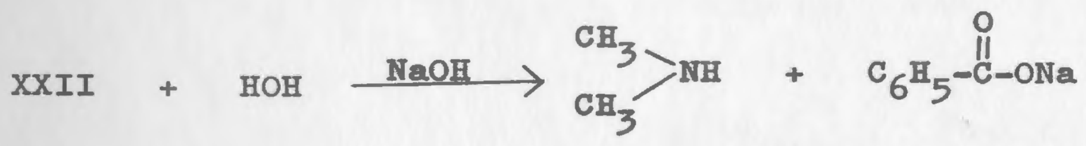


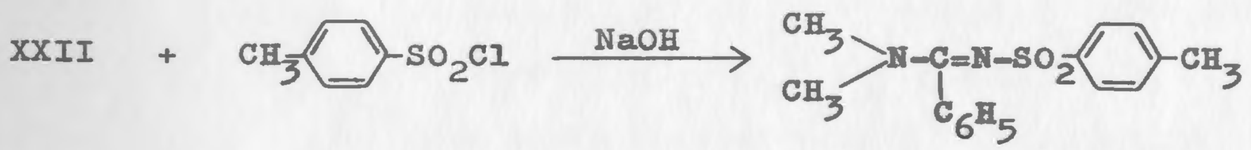
XXI



XXII

XXIII



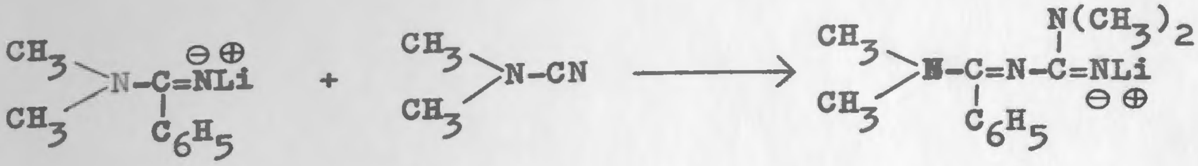


XXIV

mole of phenyllithium to one mole of dimethylcyanamide with the phenyl group becoming attached to the carbon atom of the nitrile group of the cyanamide producing an anionic nitrogen and the lithium cation. Hydrolysis of (XXI) gives N,N-dimethylbenzamidine (XXII) and lithium hydroxide. The hydrochloride of N,N-dimethylbenzamidine (XXIII) was prepared by passing hydrogen chloride gas into the solution of the amidine in absolute ether. Hydrolysis of the amidine in basic aqueous solution gave benzoic acid, and benzamide was the intermediate (12). The amidine was also converted to N,N-dimethyl-N'-p-toluenesulfonylbenzamidine (XXIV) by treating with p-toluenesulfonyl chloride under basic condition. The N.M.R., I.R., Mass spectra and microanalyses showed that this was the correct compound and its m.p. was also the same as that of the compound prepared by V. L. Dubina (13). No insoluble substance was obtained from the aqueous layer after standing overnight.

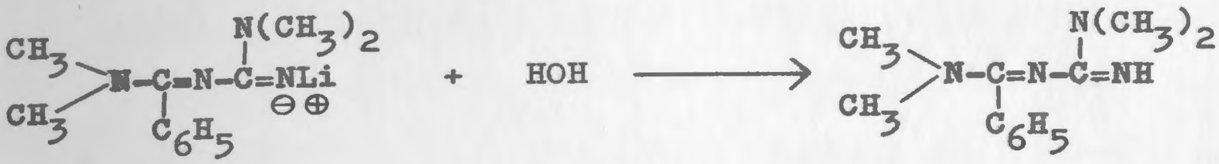
When the ratio of phenyllithium to dimethylcyanamide was 1:1, 28% of N,N-dimethylbenzamidine was obtained from the ethereal layer and 14% of 1,1-dimethyl-2-benzoylguanidine (XXVIII) was obtained from the aqueous layer. The latter compound could also be prepared by the reaction between 1,1-dimethylguanidine sulfate and benzoylchloride (14). In order to find out the precursor of 1,1-dimethyl-2-benzoylguanidine, the experiment was repeated but the ratio of phenyllithium to dimethylcyanamide was 1:1.5. After the separation of the two layers, instead of standing overnight, the aqueous layer was extracted immediately with chloroform. A brownish thick liquid was obtained. Since this thick liquid was difficult to purify then it was converted to a solid derivative by treating with p-toluenesulfonyl chloride in acetone solution and this solid derivative was identified as 1-{α-(dimethylamino)benzylidene}-3,3-dimethyl-2-p-toluenesulfonylguanidine (XXVII) by microanalysis, spectroscopy properties and its method of formation. Therefore the thick liquid substance must be 1-{α-(dimethylamino)-benzylidene}-3,3-dimethylguanidine, (XXVI), which hydrolyses slowly in the basic aqueous solution to give 1,1-dimethyl-2-benzoylguanidine (XXVIII) and dimethylamine. From the molecular structure of 1-{α-(dimethylamino)benzylidene}-3,3-dimethylguanidine it is thought that this compound is formed by hydrolysis of the lithium salt of 1-{α-(dimethylamino)benzylidene}-3,3-dimethylguanidine, (XXV), which comes from the condensation of one mole of dimethylcyanamide and one mole of the lithium salt of N,N-dimethylbenzamidine (XXI).

When the ratio of phenyllithium to dimethylcyanamide was 1:2, no N,N-dimethylbenzamidine was obtained from the ethereal layer, but a known compound 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine (XXX) was obtained in 18% yield and an impurity which always crystallised with the major product during recrystallization. This impurity was identified as the known 2,4,6-tris(dimethylamino)-1,3,5-triazine (XXXIV). 1,1-Dimethyl-2-benzoylguanidine was also obtained in 17% yield from



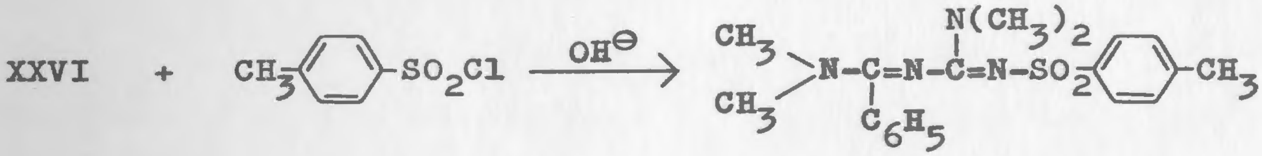
XXI

XXV

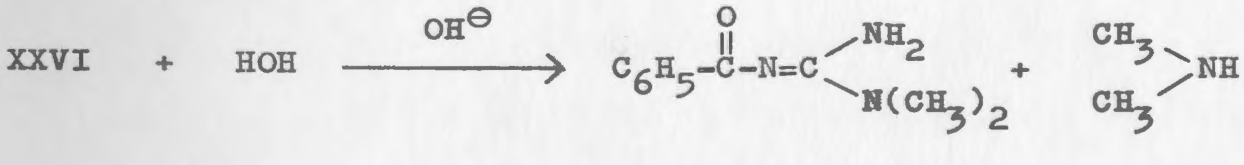


XXV

XXVI

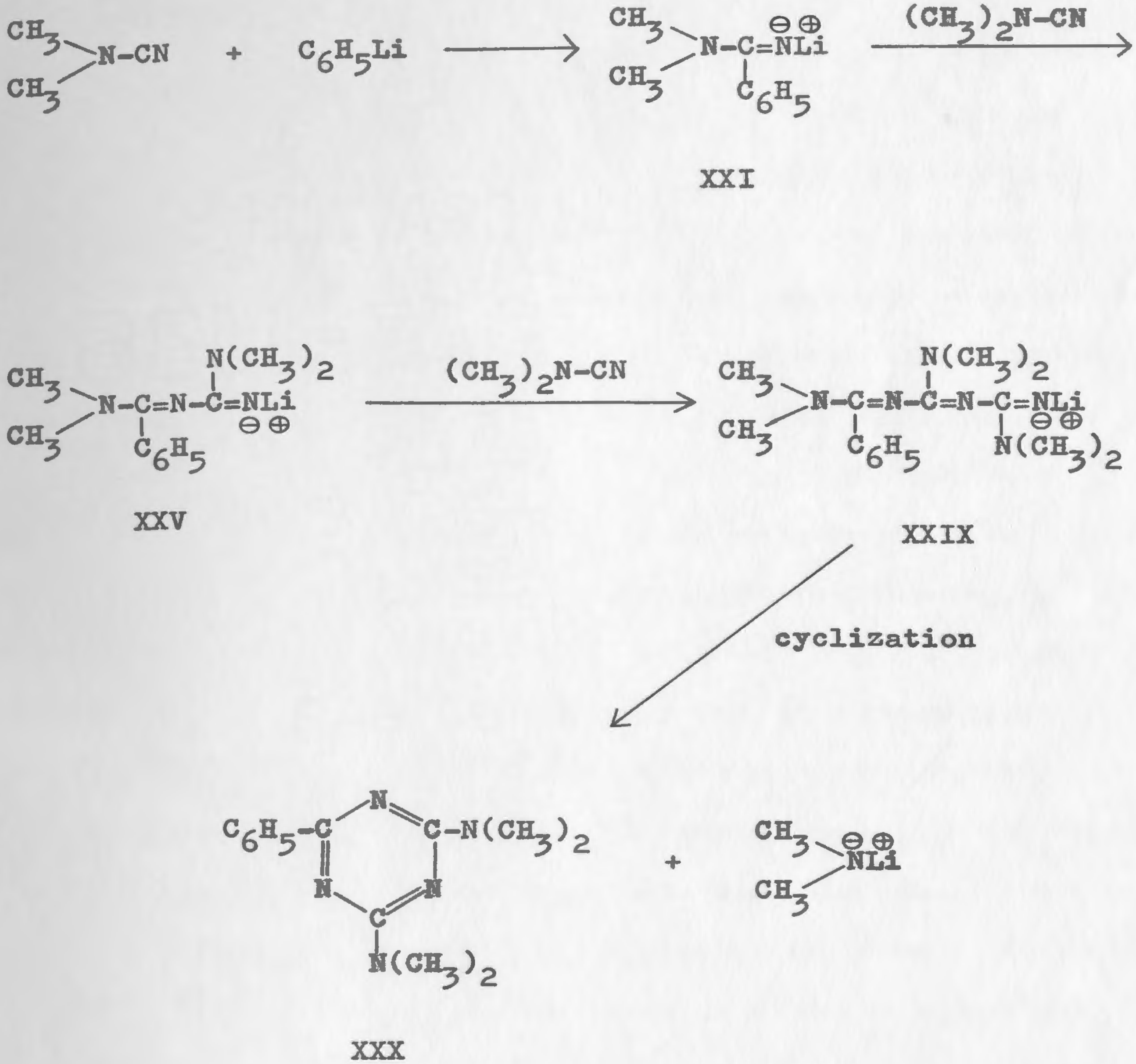


XXVII



XXVIII

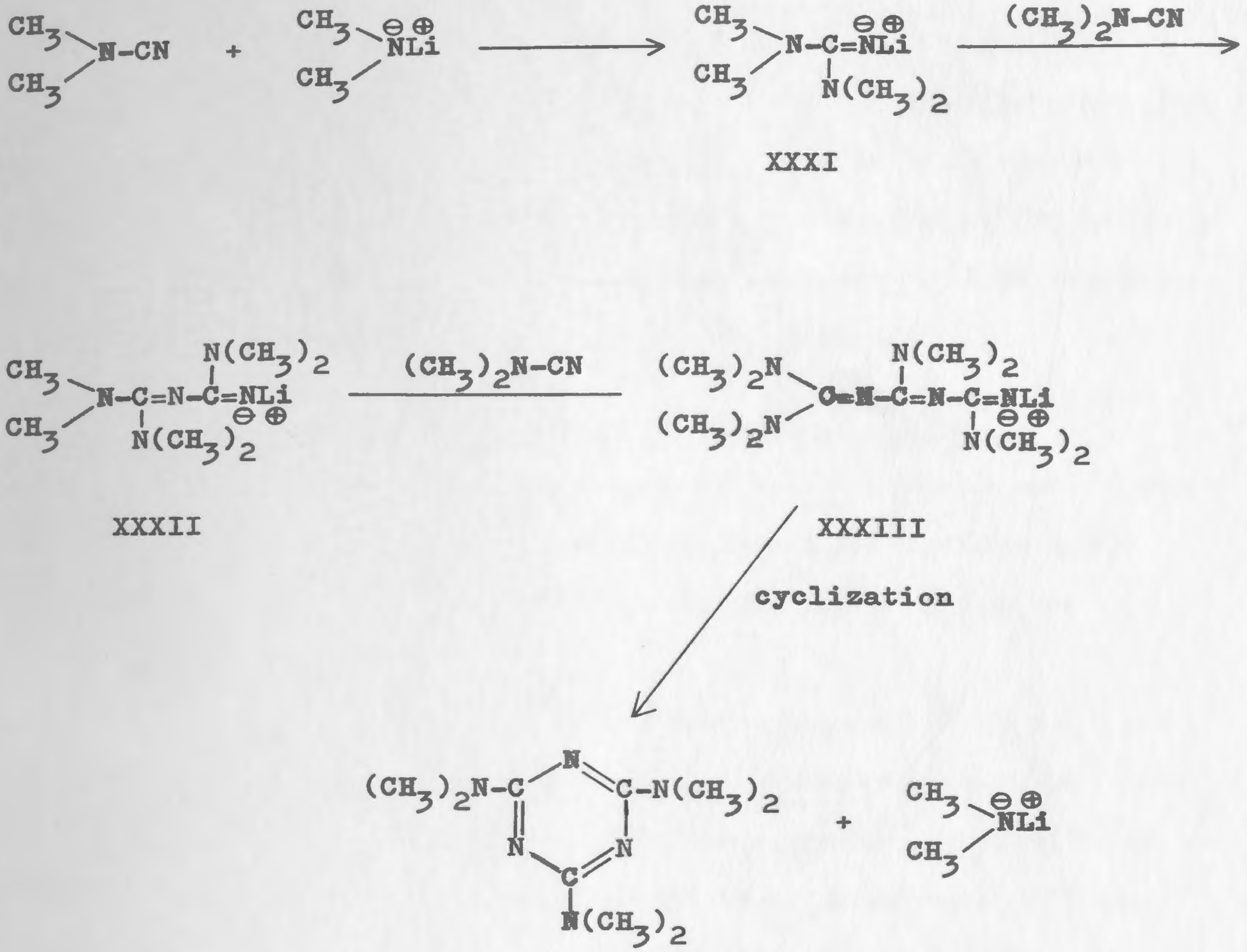
the aqueous layer after standing overnight. In order to get enough sample of 2,4,6-tris(dimethylamino)-1,3,5-triazine for analyses, the same experiment was repeated except that the ratio of phenyllithium to dimethylcyanamide was 1 : 4. The results showed that the yield of 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine increased from 18% to 38% and the yield of 2,4,6-tris(dimethylamino)-1,3,5-triazine was now 14%, but, the yield of the 1,1-dimethyl-2-benzoylguanidine was reduced to 1%. Once again, no N,N-dimethylbenzamidine was obtained from the ethereal layer of this experiment. From the products and their yields in the experiments, the mechanism of formation of 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine and 2,4,6-tris-(dimethylamino)-1,3,5-triazine can also be explained. As we have pointed out the reaction is initiated by the addition of phenyllithium to dimethylcyanamide. If the ratio of phenyllithium to dimethylcyanamide is 2 : 1, i.e. phenyllithium is in large excess, one mole of phenyllithium can only react with one mole of dimethylcyanamide to form the lithium salt of N,N-dimethylbenzamidine which gives N,N-dimethylbenzamidine on hydrolysis. If the ratio is 1 : 1, some of the lithium salt of N,N-dimethylbenzamidine condenses with another mole of dimethylcyanamide to form the lithium salt of 1-{α-(dimethylamino)-benzylidene}-3,3-dimethylguanidine, therefore the yield of N,N-dimethylbenzamidine is reduced in the experiment. If the ratio is 1 : 2, some of the lithium salt of 1-{α-(dimethylamino)-benzylidene}-3,3-dimethylguanidine condenses with one more


CH3
CH3
N-CN
+
C6H5Li
CH3
CH3
N-C=NLi
C6H5
(CH3)2N-CN
XXI
N(CH3)2
N-C=N-C=NLi
XXV
(CH3)2N-CN
N-C=N-C=N-C=NLi
N(CH3)2
XXIX
cyclization
C6H5-C
C-N(CH3)2
N(CH3)2
+
NLi
XXX

mole of dimethylcyanamide to give (XXIX) which forms 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine via an intramolecular nucleophilic substitution reaction with the elimination of one mole of lithium dimethylamide which hydrolyzes to give dimethylamine. After the formation of lithium dimethylamide in the reaction mixture, another series of reactions is initiated by this compound. The lithium dimethylamide reacts with one mole of dimethylcyanamide to form the lithium salt of 1,1,3,3-tetramethylguanidine (XXXI) which reacts with another mole of dimethylcyanamide to give (XXXII). This compound inturn condenses with one mole of dimethylcyanamide to form (XXXIII) which yields 2,4,6-tris(dimethylamino)-1,3,5-triazine via an intramolecular nucleophilic reaction with the elimination of one mole of lithium dimethylamide. Lithium dimethylamide is the catalyst of this reaction, because it enters the reaction during the first step and is regenerated at the final step. The addition of dimethylcyanamide to a solution of lithium dimethylamide in ether gave 2,4,6-tris(dimethylamino)-1,3,5-triazine in 8% yield.

In every experiment, some brownish sticky material was obtained and purification of this compound was not successful.

Attempts to carry out the experiment in dry tetrahydrofuran or dimethoxyethane were not successful because both of these solvents reacted with phenyllithium at room temperature. The experiment could be performed in dry benzene



XXXI

XXXII

XXXIII

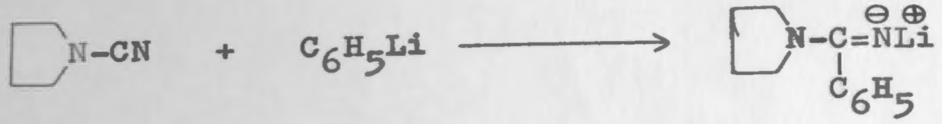
XXXIV

and the yields of 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine and 2,4,6-tris(dimethylamino)-1,3,5-triazine were 1% and 53% respectively if the ratio of the phenyllithium to dimethylcyanamide was 1 : 2. When dry hexane was used as solvent the yield of 2,4,6-tris(dimethylamino)-1,3,5-triazine was 56% and 2,6-bis(dimethylamino)-6-phenyl-1,3,5-triazine was present just as an impurity of the former.

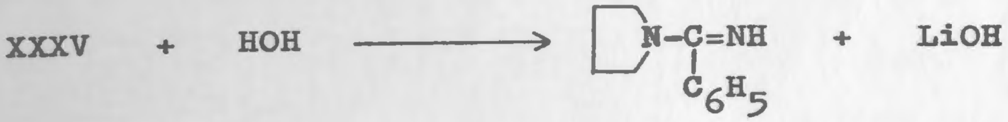
The Action of Phenyllithium on N-Cyanopyrrolidine

Because of the formation of triazines in the reaction between phenyllithium and dimethylcyanamide, we also paid the attention to the reaction between phenyllithium and N-cyanopyrrolidine.

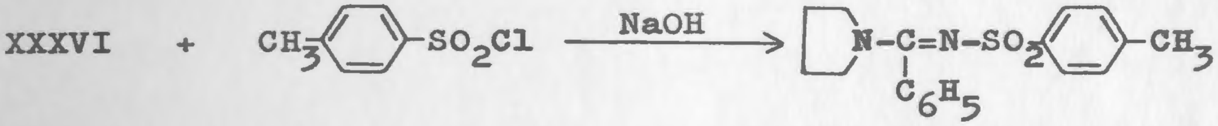
When N-cyanopyrrolidine was added to the solution of phenyllithium in absolute ether, a vigorous reaction also took place. The lithium salts of the organic compounds in the reaction mixture were hydrolyzed by cold water and the two layers separated. When the ratio of phenyllithium to N-cyanopyrrolidine was 1 : 1, a brownish thick liquid was obtained from the ethereal layer after the solvent had distilled. An attempt to purify this compound was not successful. The liquid substance was converted to a solid derivative by treating with p-toluenesulfonyl chloride in acetone and the compound was identified as N,N-tetramethylene-N'-p-toluenesulfonylbenzamidine (XXXVII) by microanalysis, spectroscopy properties and its method of formation. Therefore the precursor of



XXXV



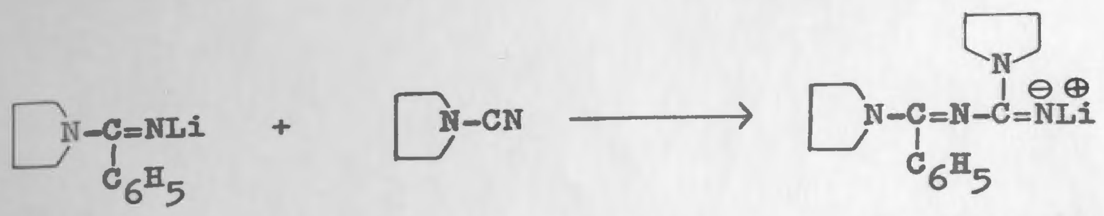
XXXVI



XXXVII

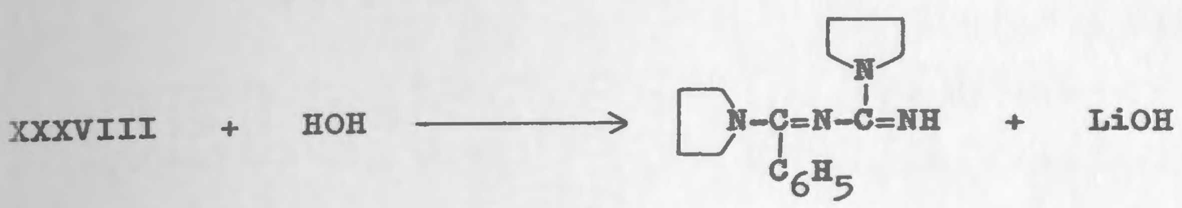
N,N-tetramethylene-N'-p-toluenesulfonylbenzamidine must have been N,N-tetramethylenebenzamidine (XXXVI) obtained in 25% yield by hydrolysis of the lithium salt of N,N-tetramethylenebenzamidine (XXXV) which formed by addition of one mole of phenyllithium to one mole of N-cyanopyrrolidine.

Instead of standing overnight, the aqueous layer was extracted with chloroform immediately and another brownish thick liquid was obtained. This liquid was also converted to a solid derivative by treating with p-toluenesulfonyl chloride in acetone. This solid substance was identified as 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethylene-2-p-toluenesulfonylguanidine (XL). Therefore the thick liquid substance obtained from the chloroform extract must have been 1-{α-(1-pyrrolidinyl)-benzylidene}-3,3-tetramethyleneguanidine (XXXIX) which was formed by hydrolysis of the corresponding lithium salt (XXXVIII). This lithium salt of 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine was formed by condensation of one mole of the lithium salt of N,N-tetramethylenebenzamidine with one mole of N-cyanopyrrolidine. The yield of 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine was 38%. If the ratio of phenyllithium to N-cyanopyrrolidine was 2:1, N,N-tetramethylenebenzamidine was the sole product and the yield was 32%. If the ratio was 1:1.5, a colourless solid compound, 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine (XLIII) was obtained in 22% yield from the ethereal layer and 12% of needle-shaped crystals of 1,1-tetramethylene-2-

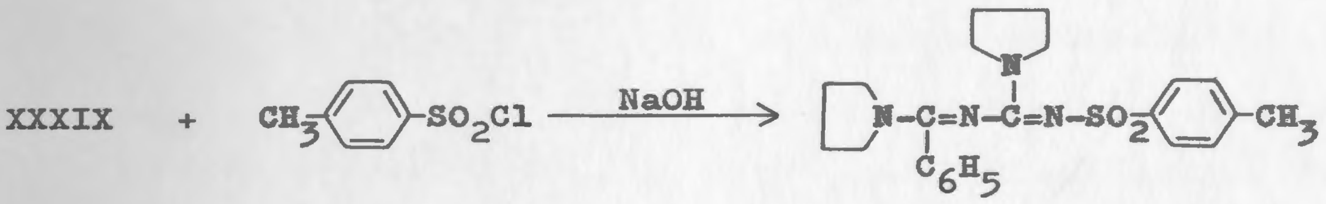


XXXV

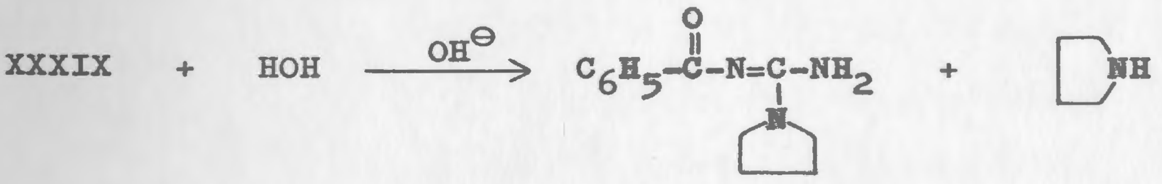
XXXVIII



XXXIX



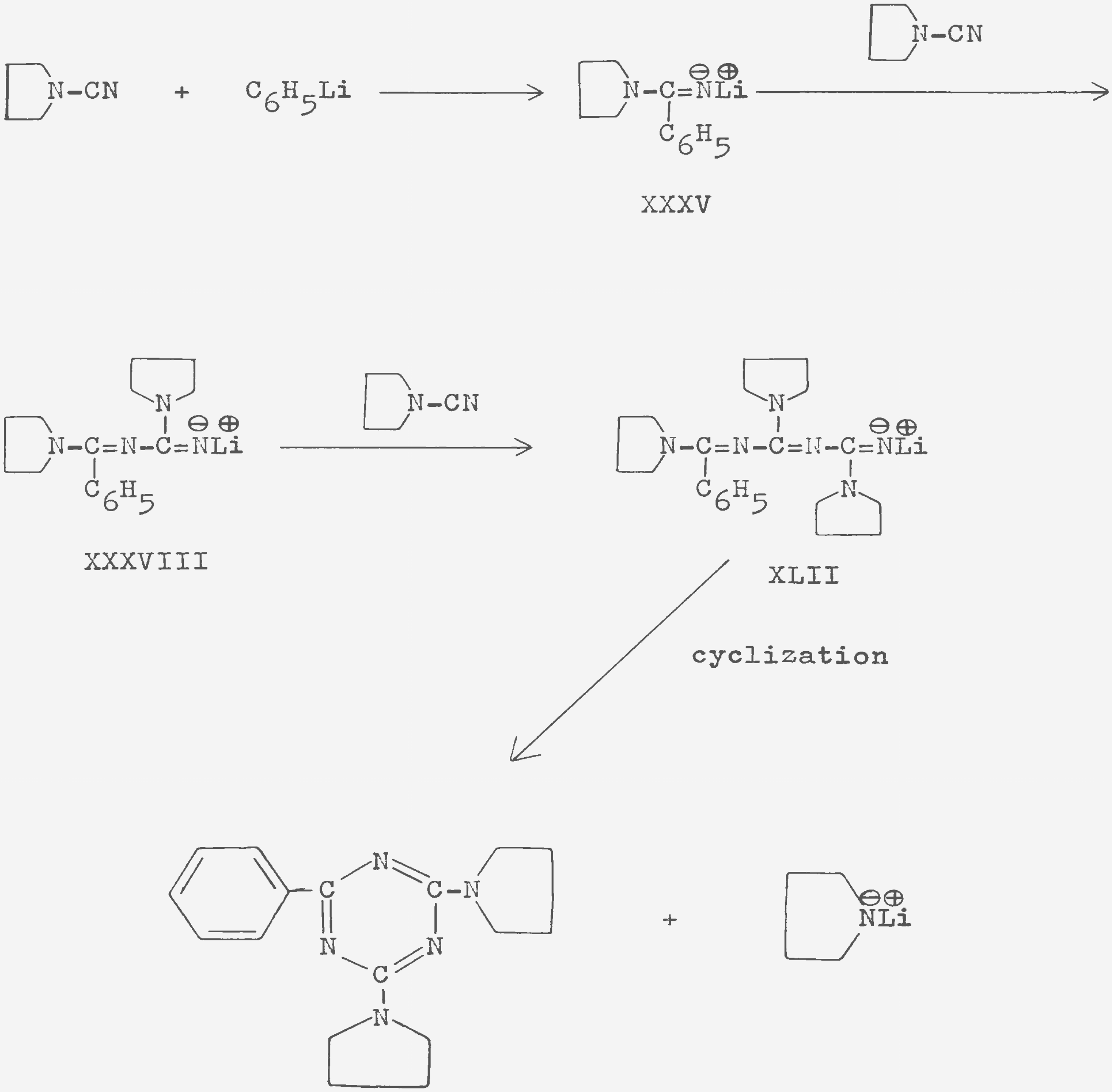
XL



XLI

benzoylguanidine (XLI) was obtained from the aqueous layer after standing overnight. From our previous experience, 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine must be the precursor of the 1,1-tetramethylene-2-benzoylguanidine. Accordingly from the intermediates and the final product, 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine, the sequence of this series of reactions can also be explained. If the ratio of phenyllithium to N-cyanopyrrolidine is 2:1, i.e. phenyllithium is in large excess, one mole of phenyllithium reacts with one mole of N-cyanopyrrolidine to form the lithium salt of N,N-tetramethylenebenzamidine (XXXV). When the ratio is 1:1, some of the lithium salt of N,N-tetramethylenebenzamidine condenses with another mole of N-cyanopyrrolidine to give the lithium salt of 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine (XXXVIII) and when the ratio is 1:2, this compound would condense with a further mole of N-cyanopyrrolidine to form (XLII) which then yields 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine (XLIII) via an intramolecular nucleophilic substitution reaction with the elimination of one mole of lithium 1-pyrrolidide.

When the ratio of phenyllithium to N-cyanopyrrolidine was 1:2.5, no crystals were obtained from the aqueous layer, but 41% of 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine and small amount of 2,4,6-tris(1-pyrrolidinyl}-1,3,5-triazine (XLVII) were present in the ethereal layer. The reaction of formation of the 2,4,6-tris(1-pyrrolidinyl}-1,3,5-triazine is

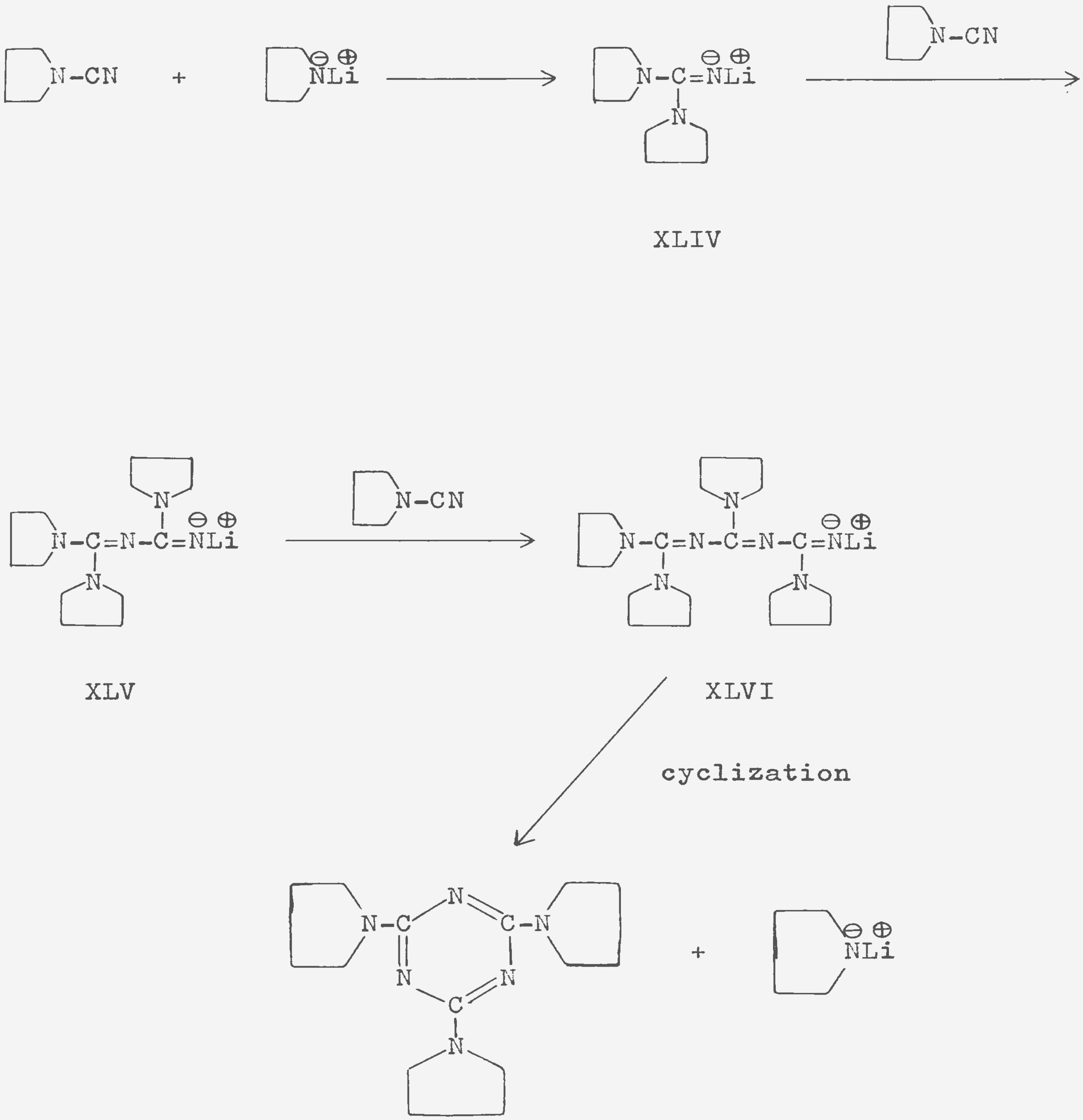

N-CN
+
C6H5Li
N-C=NLi
C6H5
XXXV
N-CN
N-C=N-C=NLi
C6H5
XXXVIII
N-CN
N-C=N-C=N-C=NLi
C6H5
XLII
cyclization
C-N
NLi
+

XLIII

thought to be initiated by lithium 1-pyrrolidide which condenses with one, two or three moles of N-cyanopyrrolidine to yield (XLIV), (XLV) and (XLVI) respectively. The last compound, (XLVI), then gives 2,4,6-tris(1-pyrrolidinyl)-1,3,5-triazine via an intramolecular nucleophilic substitution reaction with the elimination of one mole of lithium 1-pyrrolidide. The lithium 1-pyrrolidide entered the reaction during the first step and was regenerated at the final step, and therefore was a catalyst of this series of reactions.

Action of Phenyllithium on N-Methyl-N-Cyanoaniline

Lettré had carried out this same experiment in 1951, but at that time he was only interested in searching for methods of preparation of nitriles. This experiment was repeated under the same conditions and the products were examined carefully. It was surprising that besides 4% of benzonitrile, 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine (LI) was obtained in 57% yield from the interface of the ethereal and aqueous layers. After neutralization of the dilute hydrochloric acid solution which had been used to wash the ethereal layer, 7% of 1,3-dimethyl-1,3-diphenylguanidine (XLIX) was obtained. If lithium methylphenylamide was used instead of phenyllithium the yield of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine was increased to 85%, but no benzonitrile was obtained from the ethereal layer. The method of formation of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine can be explained



XLIV

XLV

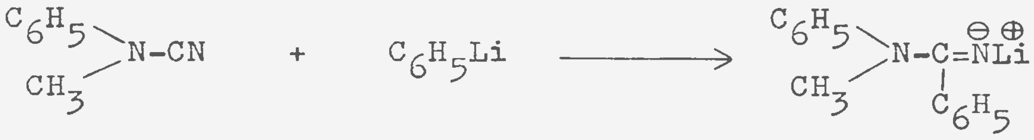
XLVI

XLVII

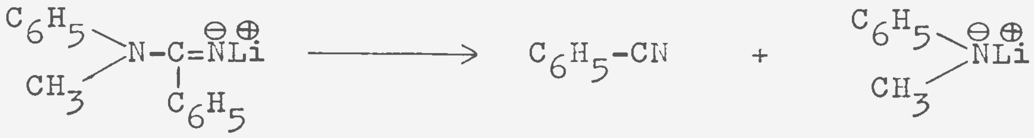
as follows. The phenyllithium reacts with one mole of N-methyl-N-cyanoaniline to form lithium N-methyl-N-phenylbenzamidine (XV) which yields benzonitrile by splitting out one mole of lithium methylphenylamide as suggested by Lettré. This lithium methylphenylamide reacts with one mole of N-methyl-N-cyanoaniline to give the lithium salt of 1,3-dimethyl-1,3-diphenylguanidine (XLVIII) which gives 1,3-dimethyl-1,3-diphenylguanidine on hydrolysis. If the lithium salt of 1,3-dimethyl-1,3-diphenylguanidine condenses with another mole of N-methyl-N-cyanoaniline, the metallic derivative (L) is formed and this compound produces 1,3-dimethyl-1,3-diphenyl-2-cyanoaniline by again splitting out one mole of lithium methylphenylamide. The lithium methylphenylamide is present in the reaction mixture as a catalyst of this reaction because it enters the reaction during the first step and is regenerated at the final step.

The tetrasubstituted guanidine was synthesized by R. L. Meek <u>et</u> <u>al</u> (15), in which 62% of the hydrobromide of 1,3-dimethyl-1,3-diphenylguanidine (LV) was obtained by the reaction between one part of cyanogen bromide and two parts of N-methylaniline. It is suggested that N-methyl-N-cyanoaniline and the hydrobromide of N-methylaniline are formed during the first step of the reaction and these two compounds condense with each other at 170 - 80° to yield (LV).

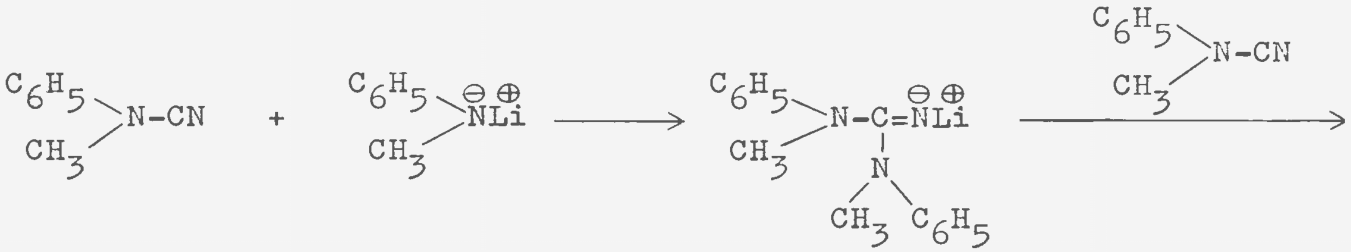
Different products can be obtained if 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine is hydrolyzed under different



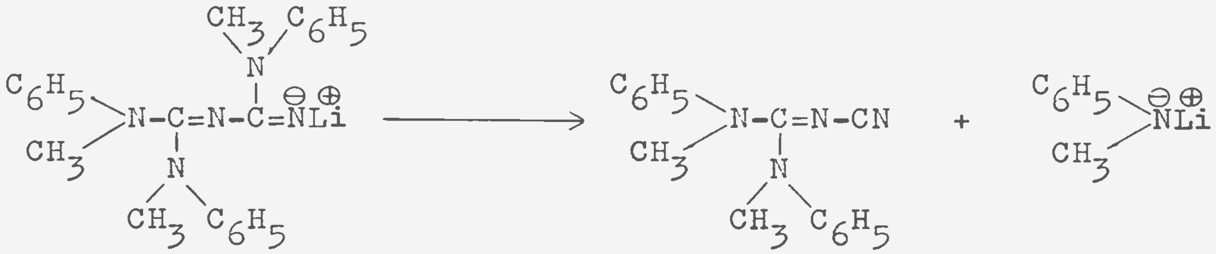
XV



XV

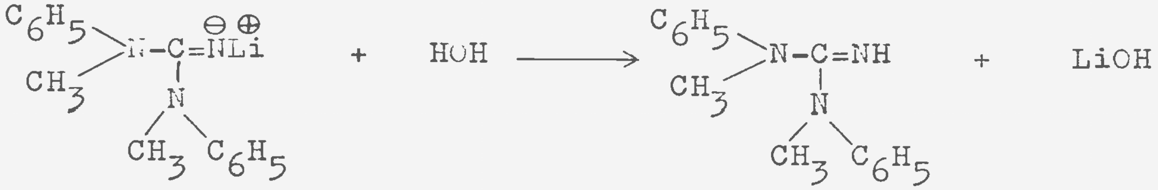


XLVIII



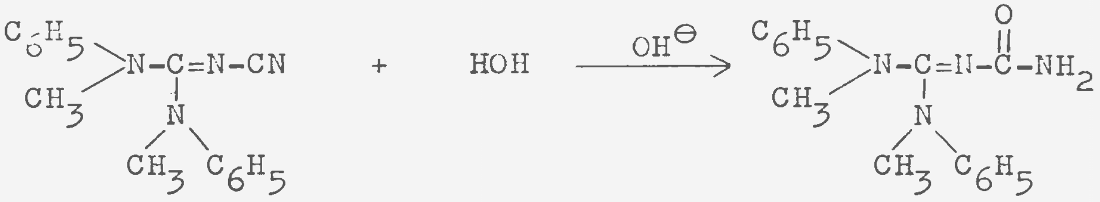
L

LI

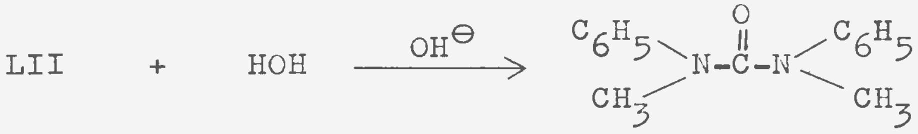


XLVIII

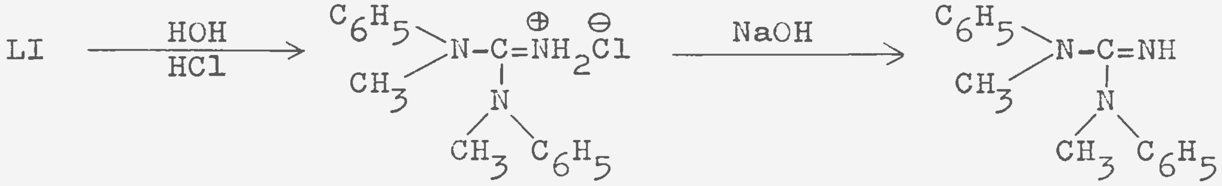
XLIX



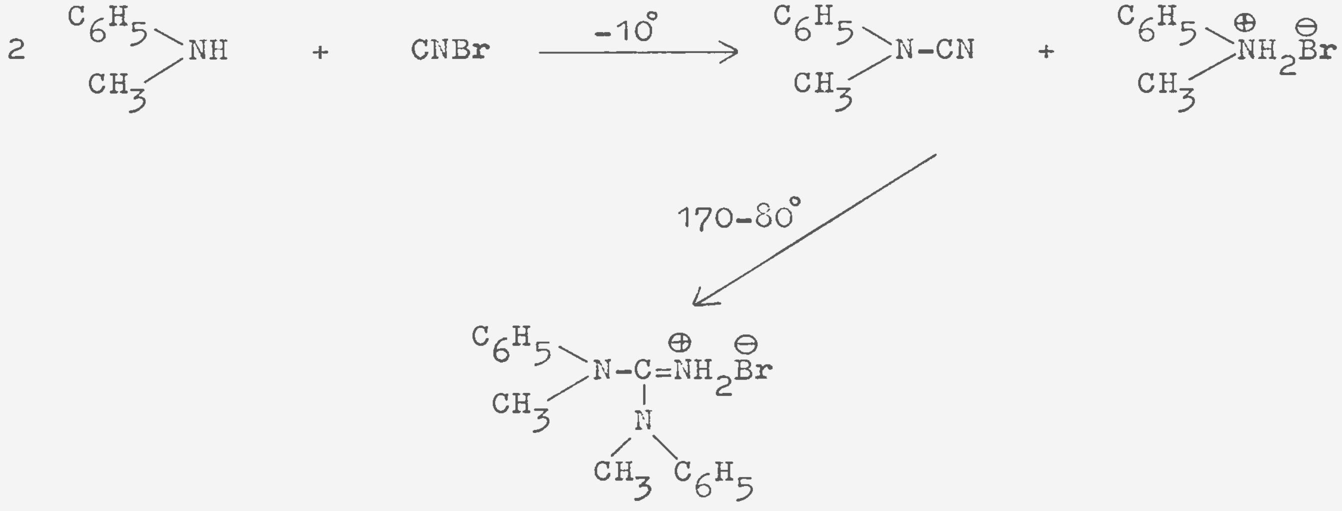
LI LII



LIII



LIV XLIX



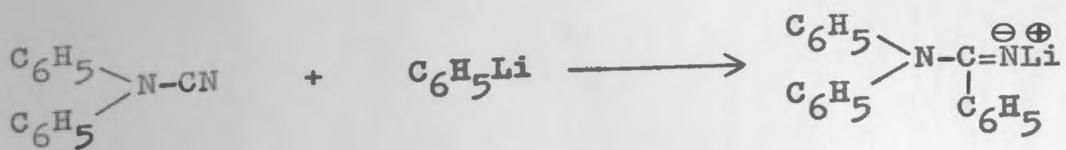
LV

conditions. When it was heated in 6N sodium hydroxide solution until the solution was clear, 1,3-dimethyl-1,3-diphenyl-2-carbamylguanidine (LII) was obtained in 80% yield; if it was refluxed in 3N sodium hydroxide solution for 48 hours N,N'-dimethyl-N,N'-diphenylurea (LIII) was obtained. If it was refluxed in 6N hydrochloric acid solution for 24 hours 86% of 1,3-dimethyl-1,3-diphenylguanidine was obtained after neutralization of the acidic solution.

The Action of Phenyllithium on Diphenylcyanamide

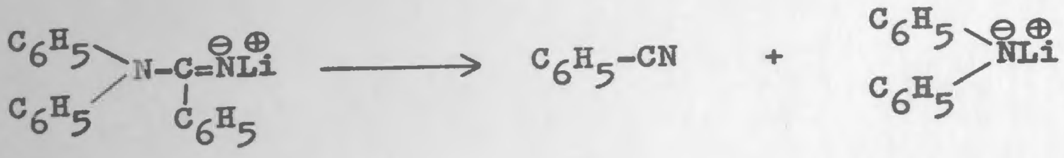
Since a new compound 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine was obtained from the reaction between phenyllithium and N-methyl-N-cyanoaniline, the reaction between phenyllithium and diphenylcyanamide was also studied under the same conditions. Benzonitrile was the sole product obtained in 10% yield. About 55% of the unreacted diphenylcyanamide was recovered. The phenyllithium reacts with one mole of diphenylcyanamide to give lithium salt of N,N-diphenylbenzamidine (LVI) which produces benzonitrile by splitting out one mole of lithium diphenylamide.

The ability to form benzonitrile from lithium salts of N-methyl-N-phenylbenzamidine and N,N-diphenylbenzamidine may be due to the ease of formation of lithium methylphenylamide and lithium diphenylamide in the ethereal solution because the anions (LVII) and (LVIII) once formed can be stabilized by delocalization of the negative charge in the ions but the



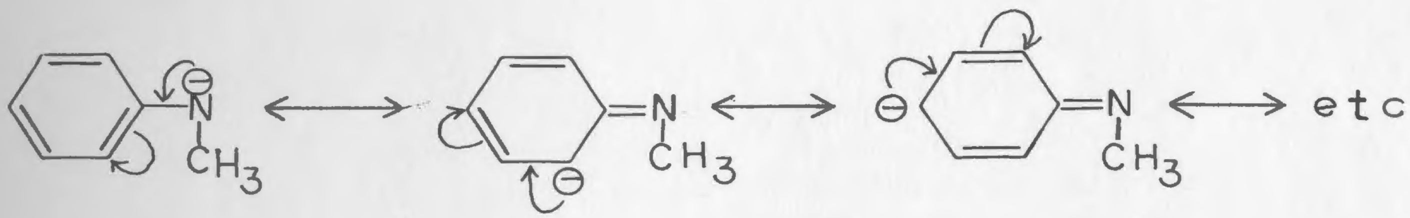
$$\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>\!N-CN + C_6H_5Li \longrightarrow \begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>\!N-\underset{\displaystyle C_6H_5}{\underset{|}{C}}=\overset{\ominus\,\oplus}{N}Li$$

LVI

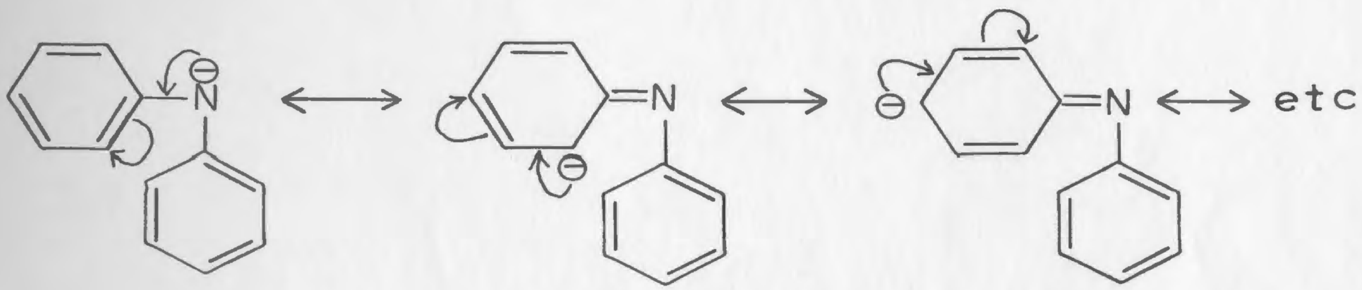


$$\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>\!N-\underset{\displaystyle C_6H_5}{\underset{|}{C}}=\overset{\ominus\,\oplus}{N}Li \longrightarrow C_6H_5-CN + \begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>\!\overset{\ominus\,\oplus}{N}Li$$

LVI



LVII



LVIII

anions from lithium dimethylamide and lithium l-pyrrolidide do not have this kind of stabilization effect therefore no benzonitrile can be produced from lithium salts of N,N-dimethylbenzamidine and of N,N-tetramethylenebenzamidine by the splitting out of a stable anion.

SPECTRA

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer as potassium chloride discs (1 mg. sample in 180 mg. KCl). Ultraviolet spectra were recorded on a Perkin-Elmer 202 Ultraviolet spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 analytical spectrometer and a Varian HA-100 spectrometer and resonance positions were reported on the τ scale, using tetramethylsilane as an internal reference. Mass spectra were recorded using a Hitachi-Perkin-Elmer RMU-6E mass spectrometer and the spectra were normalized. The value in the bracket following the mass number is the relative abundance of the ion compared with the base peak equal to 100%.

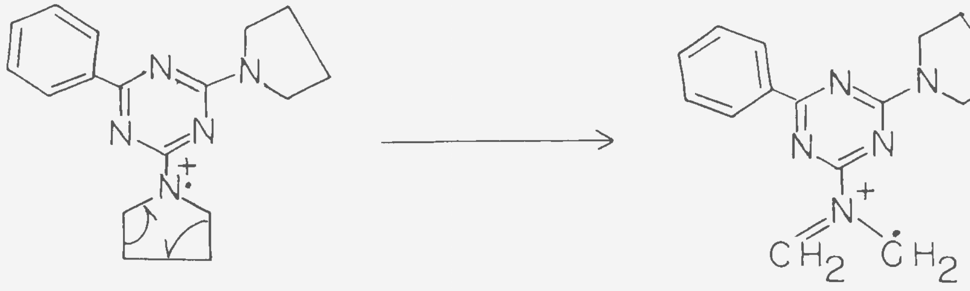
Similar compounds such as 1,1-dimethyl-2-benzoylguanidine and 1,1-tetramethylene-2-benzoylguanidine, N,N-dimethyl-N'-p-toluenesulfonylbenzamidine and N,N-tetramethylene-N'-p-toluenesulfonylbenzamidine produce similar absorption bands in their ultraviolet spectra. The molar extinction coefficients of each pair of compounds are almost the same. For example, the absorptions of the first pair of compounds are λ_{max} 243(sh, ε 9830), 268mμ(ε 16852) and λ_{max} 246(sh, ε 9228), 271mμ(ε 17057) respectively.

The infrared spectra of N,N-dimethylbenzamidine, N,N-tetramethylenebenzamidine and 1,3-dimethyl-1,3-diphenylguanidine all show a characteristic absorption at

ν_{max} 3300 cm^{-1} and the broad shape of the absorptions resemble each other. They are due to the hydrogen bonded =N-H group. 1,1-Dimethyl-2-benzoylguanidine and 1,1-tetramethylene-2-benzoylguanidine show two absorptions at the region between 3400 - 3100 cm^{-1} because both of these compounds contain a $-NH_2$ group. 1,3-Dimethyl-1,3-diphenyl-2-cyanoguanidine produces a moderately strong C≡N absorption at ν_{max} 2170 cm^{-1} which is almost at the same position as that of the absorption of 1,1,3,3-tetramethyl-2-cyanoguanidine (16). Comparison of the infrared spectra of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine and N-methyl-N-cyanoaniline shows that the absorption due to the nitrile group of the former is located at longer wavelength region than that produced by the nitrile group of the latter, because the nitrile group of the cyanoguanidine is conjugated to a C=N group which reduces its absorption frequency.

Comparison of the N. M. R. spectra of 2,4,6-tris(dimethylamino)-1,3,5-triazine and 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine shows that the absorption of the methyl group of the unsymmetrical triazine was shifted to lower field region (τ 6.78) than that of the symmetrical triazine (τ 6.90) by the phenyl group. The phenyl group also shows the same effect on both α and β pyrrolidinyl protons when comparing the spectra of 2,4,6-tris(1-pyrrolidinyl)-1,3,5-triazine and 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine. The chemical shifts of the protons of the dimethylamino group of N,N-dimethyl-N'-p-toluenesulfonylbenzamidine are not identical (τ 6.76 and 7.22) indicating that these protons are not magnetically equivalent. The protons at 2- and 5- positions of the pyrrolidinyl group of N,N-tetramethylene-N'-p-toluenesulfonylbenzamidine also show this phenomenon (τ 6.28 and 6.94).

Compounds containing dimethylamino, pyrrolidinyl or methylphenylamino group show strong peaks in the mass spectra at m/e 44, 70 or 106 respectively. Like other 1,3,5-triazines, 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine also gives strong parent peak at m/e 295. The base peak is located at m/e 267, which is due to (LX) formed by the loss of an ethylene molecule from the molecular ion (LIX). The other peaks such as m/e 226, 104 and 97 are caused by (LXI), (LXII) and (LXIII). Both 1,1-dimethyl-2-benzoylguanidine and 1,1-tetramethylene-2-benzoylguanidine show strong absorption at m/e 105 (LXV) and strong parent peaks. They also produced strong peaks at m/e 114 and 140 respectively indicating the presence of (LXVI) and (LXVIII). Both N,N-dimethyl-N'-p-toluenesulfonylbenzamidine and N,N-tetramethylene-N'-p-toluenesulfonylbenzamidine show absorptions at m/e 155 (LXIX) and 104 (LXX). They also show additional absorptions at m/e 147 (LXXI) and 173 (LXXII) respectively. The spectra of 1-{α-(dimethylamino)benzylidene}-3,3-dimethyl-2-p-toluenesulfonylguanidine and 1-{α-(tetramethylene)benzylidene}-3,3-tetramethylene-2-p-toluenesulfonylguanidine are complicated.

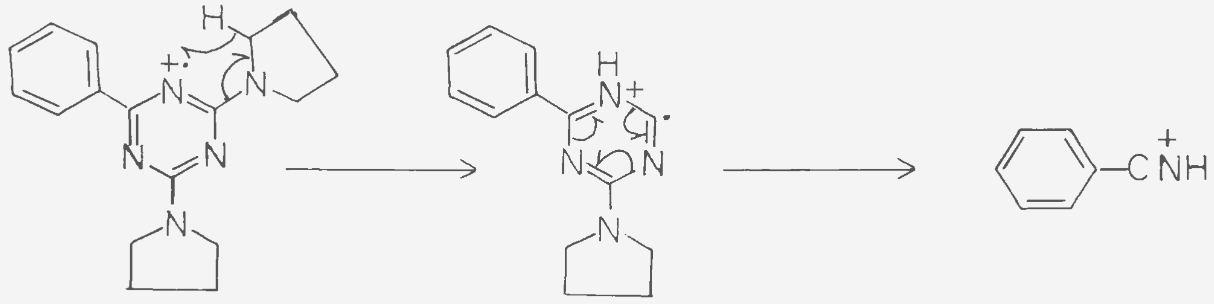


m/e 295

LIX

m/e 267

LX



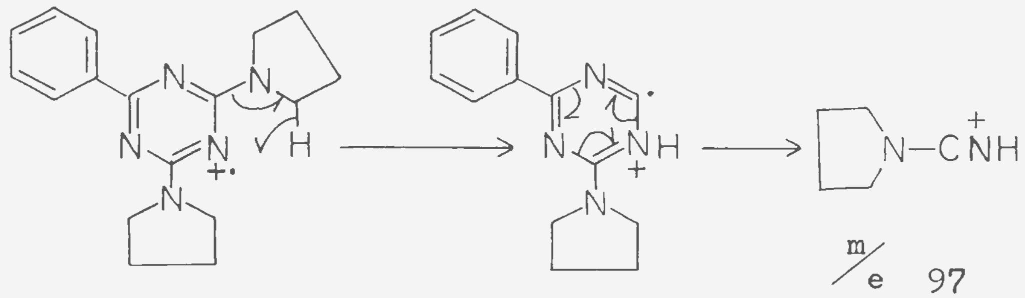
LIXa

m/e 226

LXIa

m/e 104

LXII

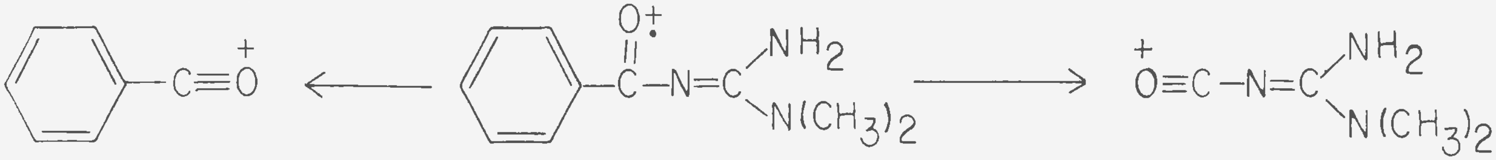


LIXb

LXIb

m/e 97

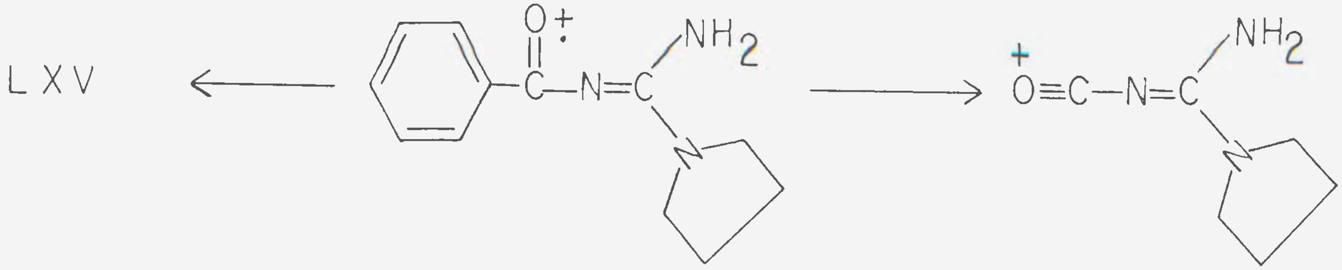
LXIII



m/e 105 LXV

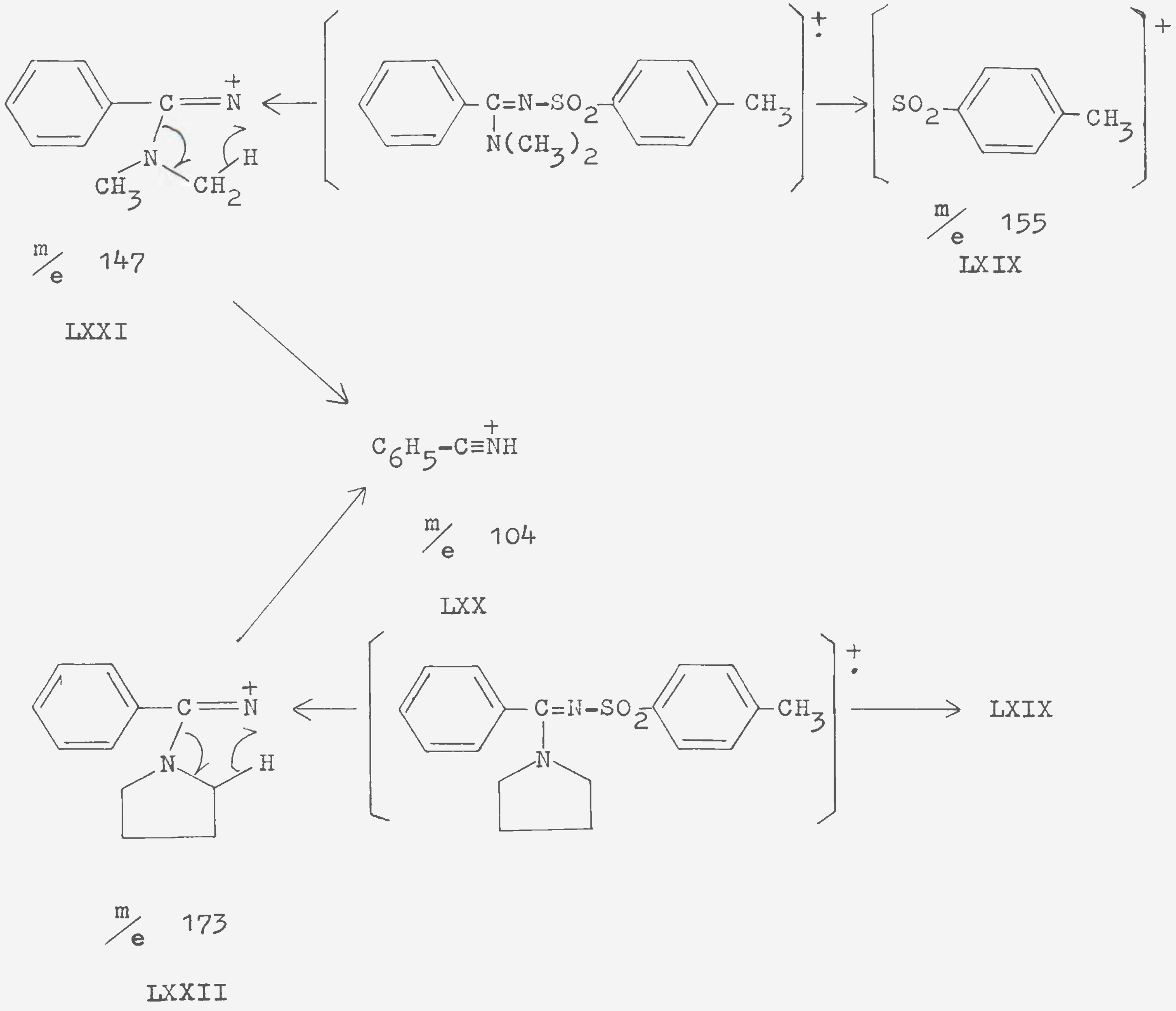
m/e 191 LXIV

m/e 114 LXVI

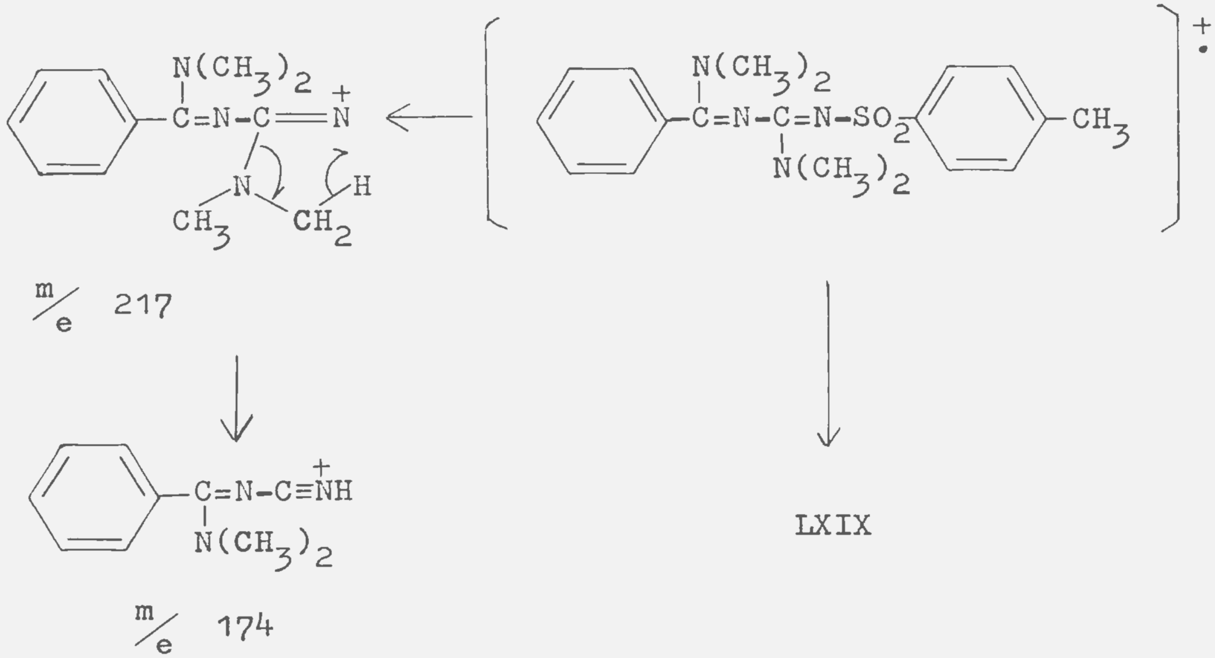


m/e 217 LXVII

m/e 140 LXVIII

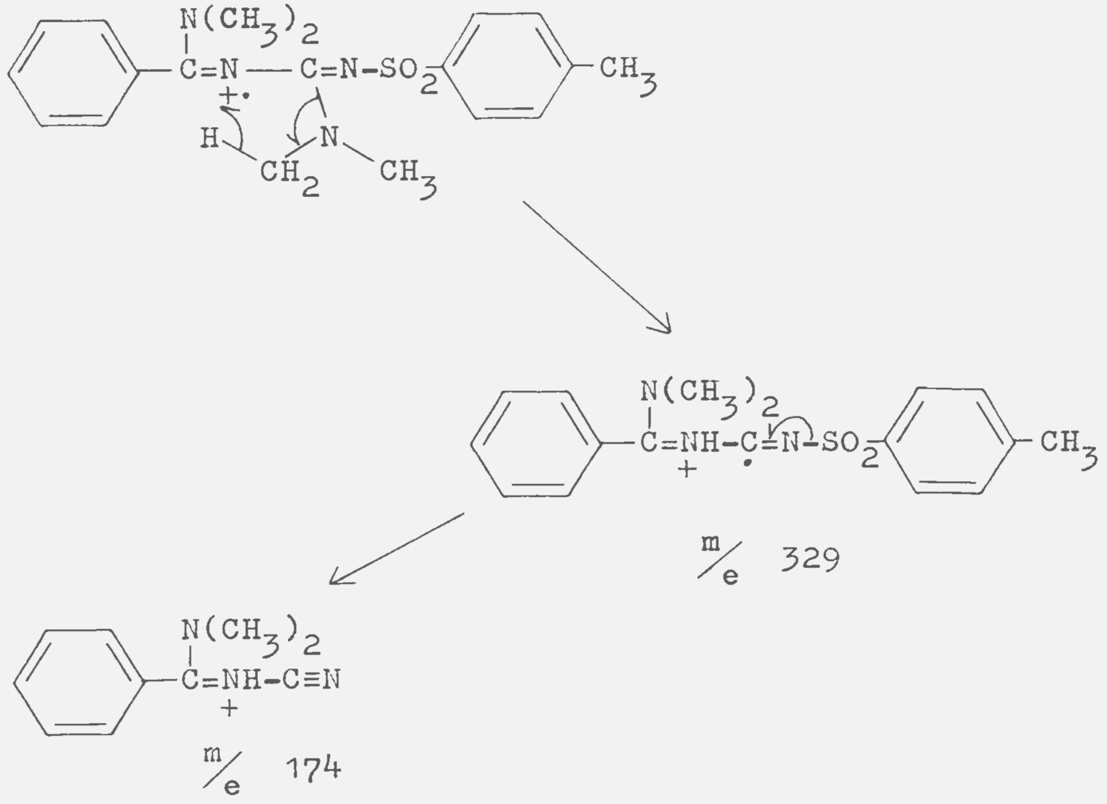

m/e 147
LXXI
m/e 155
LXIX
$C_6H_5-C\equiv\overset{+}{N}H$
m/e 104
LXX
LXIX
m/e 173
LXXII

The base peak of the first compound is at m/e 174 which is probably caused by (LXXIIIa) and (LXXIIIb) and the base peak of the second compound is probably due to (LXXIVa) and (LXXIVb). The parent peak of 1,3-dimethyl-1,3-diphenyl-2-carbamylguanidine is weak but it shows strong absorptions at m/e 238 (LXXV), 133 (LXXVI) and 107 (LXXVII). 1,3-Dimethyl-1,3-diphenyl-2-cyanoguanidine produces strong parent peak at m/e 264. The base peak, m/e 147 (LXXVIII) and the absorption at m/e 117 (LXXIX) are thought to be formed after the rearrangement of the original molecular ion. The pathway of formation of these two fragments has not been proved.

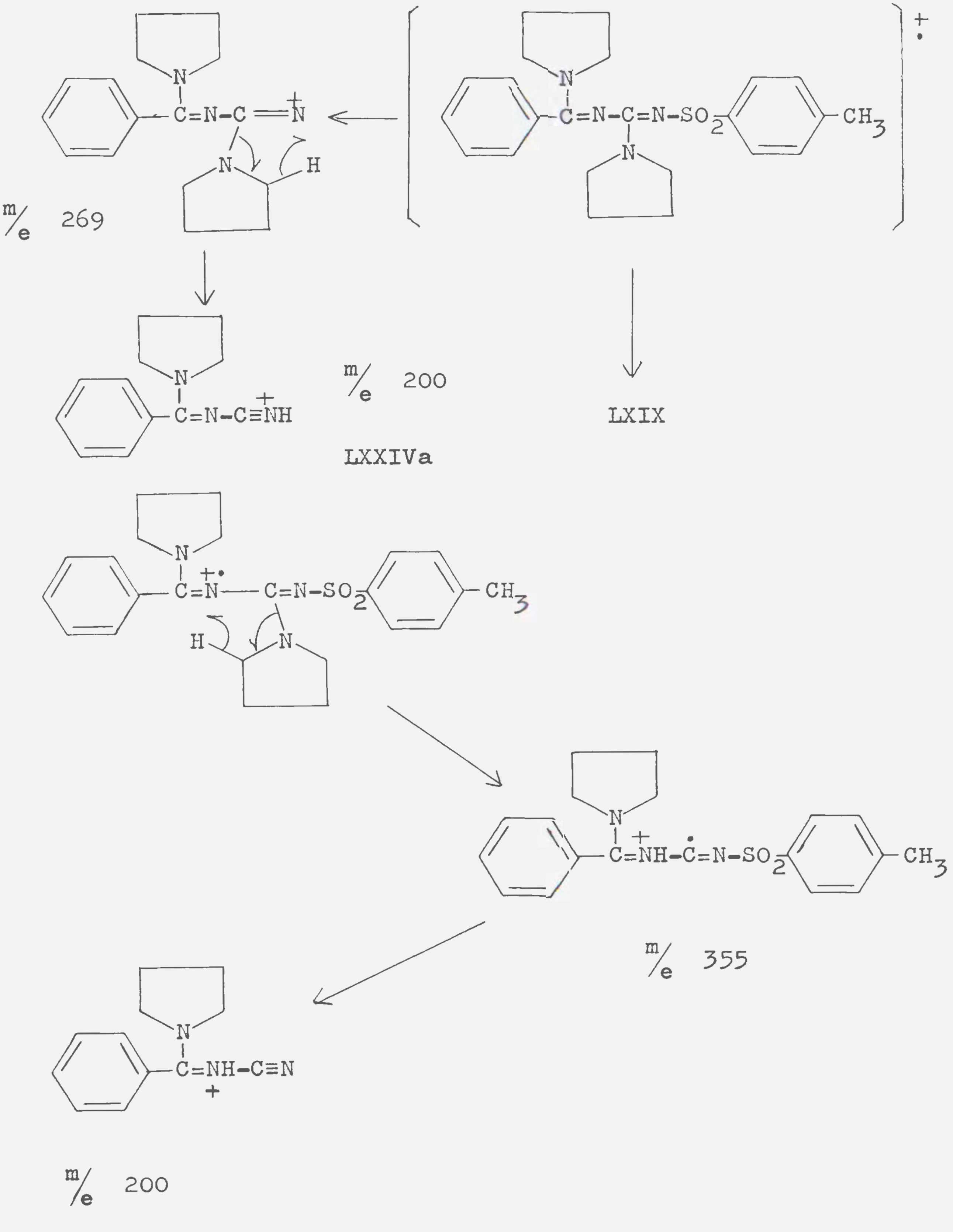


LXIX

LXXIIIa



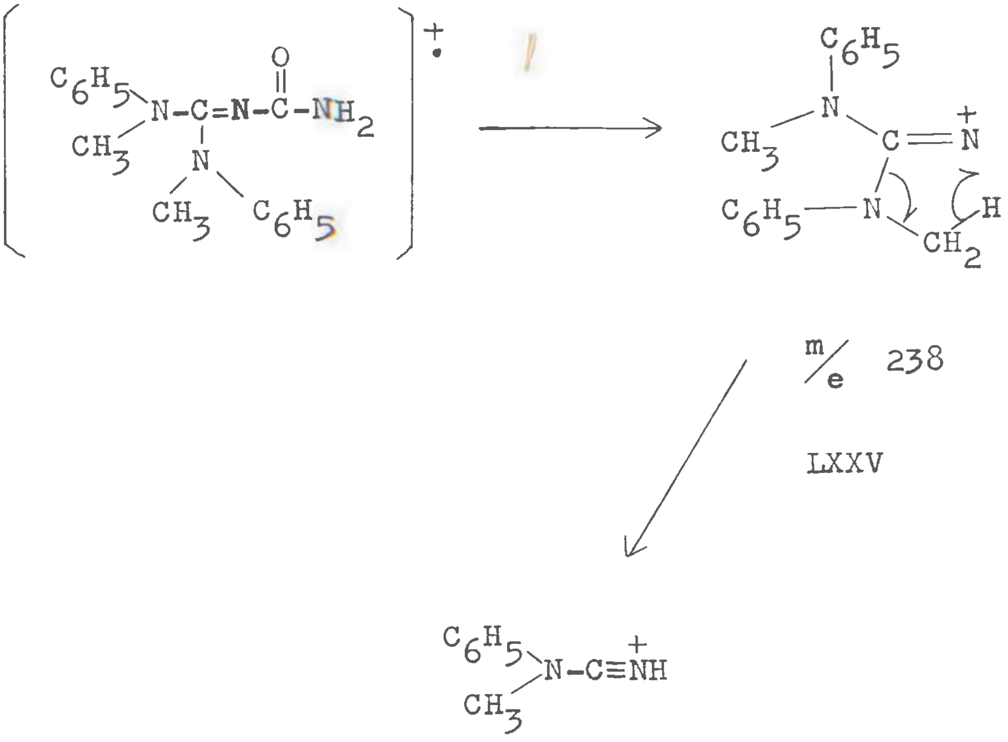
LXXIIIb



LXXIVa

LXIX

LXXIVb

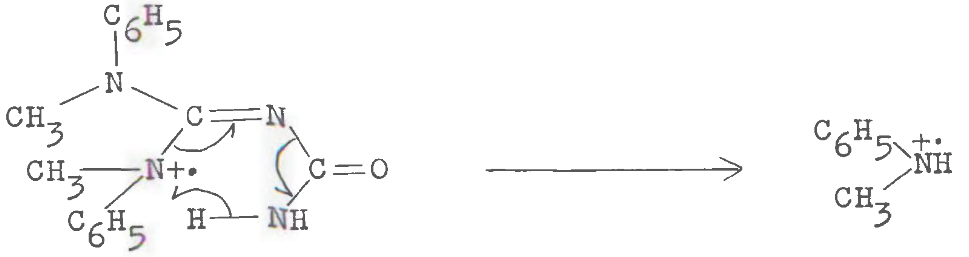


$^{m}/_{e}$ 238

LXXV

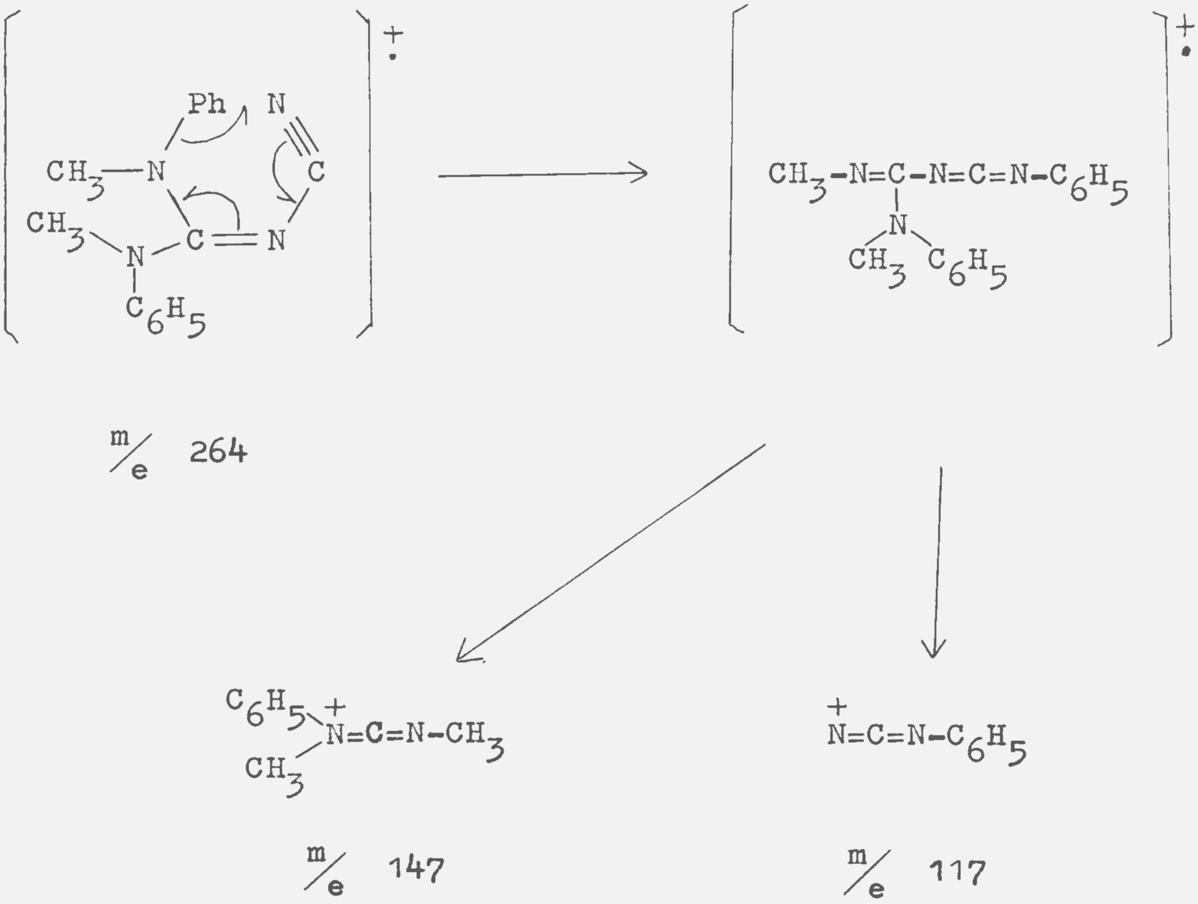
$^{m}/_{e}$ 133

LXXVI



$^{m}/_{e}$ 107

LXXVII



LXXVIII

LXXIX

1,1-Dimethyl-2-benzoylguanidine

Ultraviolet spectrum (methanol): λ_{max} 243 (sh, ε 9830), 268mμ (ε 16852).

Infrared spectrum: ν_{max} 3290m, 3150m, 1630m, 1590s, 1575s, 1540s, 1470m, 1450m, 1425s, 1400m, 1350s, 1240m, 1175w, 1050m, 1025w, 975w, 940w, 890w, 820w, 760w, 710w cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 1.78 (multiplet), 2.22 (singlet, broad), 2.62 (multiplet), 6.94 (singlet).

Mass spectrum: m/e 42(8), 43(14), 44(100), 45(11), 46(27), 50(7), 51(19), 69(18), 71(8), 77(53), 78(10), 105(53), 106(6), 114(67), 147(14), 148(11), 163(29), 190(12), 191(48), 192(9).

1,1-Tetramethylene-2-benzoylguanidine

Ultraviolet spectrum (methanol): λ_{max} 246 (sh, ε 9228), 271mμ (ε 17057).

Infrared spectrum: ν_{max} 3290m, 3140m, 2950w, 2930w, 2875w, 2850w, 1625m, 1590s, 1560s, 1525s, 1445s, 1425m, 1360m, 1340s, 1325s, 1290m, 1250m, 1200w, 1160m, 1140m, 1120w, 1100m, 1060w, 1025w, 890w, 750w, 720w cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 1.75 (multiplet), 2.35 (singlet, broad), 2.62 (multiplet), 6.48 (overlapping triplets), 8.08 (overlapping quintets).

Mass spectrum: m/e 41(6), 42(6), 43(14), 51(11), 55(7), 69(7), 70(100), 71(7), 77(32), 78(7), 84(6), 105(27), 140(26), 147(7), 188(14), 189(13), 217(31).

N,N-Dimethyl-N'-p-toluenesulfonylbenzamidine

Ultraviolet spectrum (methanol): λ_{max} 245mμ (ε 18947).

Infrared spectrum: ν_{max} 3040w, 3005w, 2900w, 1600w, 1585m, 1550s, 1510m, 1485m, 1450m, 1420m, 1405m, 1280s, 1270m, 1225w, 1180w, 1165w, 1150s, 1115w, 1095s, 1025w, 945w, 925m, 870s, 825w, 775w, 720w, 715w, 700w, 680s cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 2.65 (overlapping multiplets), 6.76 (singlet), 7.22 (singlet), 7.62 (singlet).

Mass spectrum: m/e 42(5), 43(5), 44(100), 65(11), 77(8), 91(48), 92(7), 104(24), 147(33), 148(5), 155(17), 302(2, parent peak).

N,N-Tetramethylene-N'-p-toluenesulfonylbenzamidine

Ultraviolet spectrum (methanol): λ_{max} 248mμ (ε 18974).

Infrared spectrum: ν_{max} 3050w, 2965w, 2900w, 2860w, 1575w, 1525s, 1450s, 1440s, 1340m, 1335m, 1275s, 1225m, 1200m, 1160w, 1140s, 1075s, 1025w, 975w, 925w, 850m, 830s, 810m, 720m, 690m cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 2.70 (overlapping multiplets), 6.28 (triplet), 6.94 (triplet), 7.62 (singlet), 8.10 (overlapping multiplets).

Mass spectrum: m/e 65(8), 66(13), 70(100), 71(8), 77(6), 91(30), 104(15), 155(10), 173(31), 328(3, parent peak).

1-{α-(Dimethylamino)benzylidene}-3,3-dimethyl-2-p-toluenesulfonylguanidine

Ultraviolet spectrum (methanol): λ_{max} 239mμ (ε 20773).

Infrared spectrum: ν_{max} 3050w, 2900w, 1585s, 1570s, 1530m, 1490m, 1460m, 1425w, 1380s, 1275s, 1220w, 1190w, 1140s, 1095m, 875m, 825w, 790w, 760w, 720w, 695w, 670w cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 2.50 (overlapping multiplets), 7.02 (singlet), 7.22 (singlet), 7.65 (singlet).

Mass spectrum: m/e 44(10), 65(5), 71(13), 77(7), 91(45), 92(5), 104(7), 118(7), 125(5), 147(5), 155(27), 173(7), 174(100), 175(14), 217(9), 326(6), 328(39), 329(9), 371(11), 372(9).

1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethylene-2-p-toluenesulfonylguanidine

Ultraviolet spectrum (methanol): λ_{max} 237mμ (ε 21948).

Infrared spectrum: ν_{max} 3040w, 2950w, 2910w, 2850w, 1610m, 1590s, 1575s, 1495s, 1475s, 1450s, 1400s, 1335m, 1290w, 1275m, 1235m, 1190w, 1145s, 1095m, 1075w, 1025w, 920w, 875m, 840w, 825w, 780w, 770m, 725w, 720w, 690w, 665m cm^{-1}.

N. M. R. spectrum: τ 2.40 (overlapping multiplets), 6.70 (overlapping multiplets), 7.62 (singlet), 8.08 (quintet), 8.32 (quintet).

Mass spectrum: m/e 41(9), 42(6), 43(7), 44(48), 55(16), 65(9), 70(84), 71(6), 77(10), 91(62), 92(7), 97(61), 163(6), 104(32), 129(10), 149(8), 155(20), 173(8), 198(6), 199(9), 200(100), 201(16), 269(57), 270(12), 354(34), 355(9), 423(10), 424(4, parent peak).

2,4-Bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine

Ultraviolet spectrum (methanol): λ_{max} 237mμ (ε 46510).

Infrared spectrum: ν_{max} 2960w, 2940w, 2860w, 1590m, 1580m, 1550s, 1520s, 1490m, 1475s, 1460s, 1385m, 1350m, 1340w, 1250w, 1225w, 1160w, 1135w, 1065w, 1025w, 1010w, 910w, 875w, 820w, 780w, 705w cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 1.55 (multiplet), 2.58 (multiplet), 6.34 (triplet), 8.08 (quintet).

Mass spectrum: m/e 41(12), 42(10), 43(6), 55(26), 68(16), 69(11), 70(30), 77(13), 78(6), 80(17), 94(6), 95(13), 96(5), 97(15), 103(7), 104(15), 122(10), 123(5), 129(14),163(5), 170(5), 197(14), 198(9), 212(5), 224(5), 225(13), 226(43), 227(9), 238(15), 239(31), 240(20), 253(12), 254(8), 266(33), 267(100), 268(62), 294(14), 295(94), 296(20).

1,3-Dimethyl-1,3-diphenyl-2-cyanoguanidine

Ultraviolet spectrum (methanol): λ_{max} 258mμ (ε 21224).

Infrared spectrum: ν_{max} 3000w, 2170s, 1580w, 1535s, 1480s, 1445w, 1420m, 1385m, 1325w, 1275w, 1225w, 1125w, 1100w, 1075w, 760w, 730w, 690m cm^{-1}.

N. M. R. spectrum ($CDCl_3$): τ 2.92 (multiplet), 3.25 (multiplet), 6.64 (singlet).

Mass spectrum: m/e 51(17), 65(10), 77(57), 78(7), 79(5), 91(10), 104(7), 106(30), 107(12), 117(23.5), 118(6), 131(6), 132(24), 133(10), 143(5), 147(100), 148(13), 158(23), 263(11), 264(30).

1,3-Dimethyl-1,3-diphenyl-2-carbamylguanidine

Ultraviolet spectrum (methanol): λ_{max} 256mμ (ε 19094).

Infrared spectrum: ν_{max} 3300m(broad), 3150m, 1675m, 1600m, 1585w, 1560s, 1495m, 1475w, 1440w, 1400w, 1365s, 1335w, 1315w, 1220w, 1125m, 1100w, 765w, 735w, 700w cm^{-1}.

N. M. R. spectrum (d_6DMSO): τ 3.00 (multiplet), 3.82 (singlet, broad), 6.90 (singlet).

Mass spectrum: m/e 42(11), 43(41), 44(7), 50(5), 51(15), 52(5), 65(14), 77(34), 78(9), 79(14), 91(16), 92(15), 104(7), 106(77), 107(100), 118(12), 131(5), 132(12), 133(30), 147(12), 182(6), 238(41), 239(14), 282(3, parent peak).

Note: The mass spectra were obtained using a direct inlet system. The variation of total ion current during the spectrum of each compound was less than 6%.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Elemental analysis were determined by Alfred Bernhardt, West Germany.

The following compounds were prepared as starting materials for the experimental work. Given with the name of each compound is the number of the literature reference.

Compound	Literature
Cyanogen bromide	17
Phenyllithium	18
Dimethylcyanamide	19
N-Cyanopyrrolidine	20
N-Methyl-N-cyanoaniline	21
Diphenylcyanamide	22

(a) 2,4,6-Tris(dimethylamino)-1,3,5-triazine, 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine and 1,1-dimethyl-2-benzoylguanidine.

The reaction vessel was a 1-litre three-necked round bottom flask, equipped with mechanical stirrer, reflux condenser (with calcium chloride drying tube at the top) and Claisen addition tube. To one mouth of the Claisen addition tube a dropping funnel was attached and dry nitrogen gas was passed through the other mouth throughout the reaction. A solution of 2.1 g. (0.025 mole) of phenyllithium in 40 ml.

of absolute ethyl ether was transferred to the three-necked flask. A solution of 7 g. (0.1 mole) of dimethylcyanamide in 40 ml. of absolute ethyl ether was added to the phenyllithium solution at such a rate that it maintained the solution at reflux. After the addition was completed, the brownish solution was refluxed for 15 minutes and then cooled in an ice bath. Finally, 80 g. of cold water was added slowly from the dropping funnel to hydrolyze the organolithium compounds. During the addition of water, white precipitates were observed, which gradually dissolved in the aqueous layer. The two layers were stirred for another 10 minutes, then the aqueous layer was separated and extracted twice with equal volumes of ether. The combined ether extract was dried over anhydrous magnesium sulfate. The ether was removed by distillation and the unreacted materials were vacuum distilled. Colourless crystals were obtained from isopropyl alcohol, m.p. 92 - 110^0. Thin layer chromatography on silica gel showed that it was a mixture of 2,4,6-tris(dimethylamino)-1,3,5-triazine and 2,4-bis-(dimethylamino)-6-phenyl-1,3,5-triazine. After recrystallization from N,N-dimethylformamide, a pure sample of 2,4,6-tris-(dimethylamino)-1,3,5-triazine was obtained, m.p. 172.5 - 3^0, literature m.p. 172 - 4^0 (23), yield 14%. Analysis, calculated for $C_9H_{18}N_6$: C, 51.40; H, 8.63; N, 39.97; found: C, 51.52; H, 8.77; N, 40.12. A pure sample of 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine could be separated from the mixture by passing it through a silica gel column, eluting with chloroform, m.p. 103 - 3.5°, literature m.p. 105 - 6° (24), yield 38%. Analysis, calculated for $C_{13}H_{17}N_5$: C, 64.17; H, 7.04; N, 28.79; found: C, 64.31; H, 6.90; N, 28.79.

After standing overnight, needle-shaped crystals of 1,1-dimethyl-2-benzoylguanidine were obtained from the water layer. This was purified by recrystallization from benzene, m.p. 163 - 4°, literature m.p. 164 - 5° (14), yield 1%. Analysis, calculated for $C_{10}H_{13}N_3O$: C, 62.80; H, 6.85; N, 21.98; found: C, 63.05; H, 6.86; N, 21.92.

When the ratio of dimethylcyanamide to phenyllithium was 2 : 1, and the experiment was carried out in an ice bath, the yields of 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine and 1,1-dimethyl-2-benzoylguanidine were 18% and 17% respectively.

(b) N,N-Dimethylbenzamidine

The procedure of this experiment was the same as that of the general method previously described in section (a), except for the steps described below. The ratio of dimethylcyanamide to phenyllithium was 1 : 1. The distillate, collected under reduced pressure, was dissolved in 80 ml. of ether then extracted with an equal volume of 3N hydrochloric acid solution. The acidic solution was cooled in an ice bath and neutralized with 6N sodium hydroxide solution and finally the solution was made strongly basic by adding 5 ml. in excess. This basic solution was extracted twice with equal volumes of ether and the combined ether extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the N,N-dimethylbenzamidine vacuum distilled, b.p. 76 - 8° at 1 mm. pressure, yield 28%. Vuylsteke (5) reported b.p. 118° at 11 mm. pressure. An authentic sample was prepared by the method of Vuylsteke. The IR spectra of these two specimens were identical. 1,1-Dimethyl-2-benzoylguanidine was also obtained from the aqueous layer, yield 14%.

When the ratio of dimethylcyanamide to phenyllithium was 1 : 2, the only product from this experiment was N,N-dimethylbenzamidine in 38% yield.

(c) N,N-Dimethyl-N'-p-toluenesulfonylbenzamidine.

A solution of 1 g. (0.0068 mole) of N,N-dimethylbenzamidine in 5 ml. of pyridine was prepared in a 50 ml. conical flask. To this solution, a solution of 2.6 g. (0.0135 mole) of p-toluenesulfonyl chloride in 15 ml. of pyridine was added slowly with stirring and cooling. The yellowish solution was allowed to stand overnight and poured into a 150 ml. ice-water mixture. The aqueous solution was stirred for an hour. The crude N,N-dimethyl-N'-*p*-toluenesulfonylbenzamidine produced was filtered and washed several times with cold water. A pure sample could be obtained by recrystallization from a solution of dimethoxyethane in a small amount of water, m.p. 161 - 2°, literature m.p. 161-2° (13), yield 40%. Analysis, calculated for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26; S, 10.58; found: C, 63.68; H, 6.09; N, 9.14; S, 10.52.

(d) 1-{α-(Dimethylamino)benzylidene}-3,3-dimethylguanidine and 1-{α-(dimethylamino)benzylidene}-3,3-dimethyl-2-p-toluenesulfonylguanidine.

Crude 1-{α-(dimethylamino)benzylidene}-3,3-dimethylguanidine was obtained by the general method previously described in section (a) except for the steps described below and that the ratio of the dimethylcyanamide to phenyllithium was 1.5 : 1. After it had been extracted with ether, instead of standing overnight, the aqueous layer was immediately extracted twice with equal volumes of chloroform. The combined chloroform extract was washed with cold water and dried over anhydrous magnesium sulfate. After removing the solvent the crude product was kept in a desiccator, yield 4.52 g. (42%).

To a cold solution of 4.52 g. (0.021 mole) of crude 1-{α-(dimethylamino)benzylidene}-3,3-dimethylguanidine in 16 ml. of acetone was added, with stirring, a solution of 4.2 g. (0.022 mole) p-toluenesulfonyl chloride in minimum of acetone and the reaction mixture was stirred for 10 minutes. After addition of 2 g. of 50% sodium hydroxide solution and 5 ml. of water, the solution was stirred for 20 minutes longer. Finally, 100 ml. of ice-cold water was added slowly and the solution was stirred for another 20 minutes. The precipitate was filtered out and washed several times with cold water. A sample of 1-{α-(dimethylamino)benzylidene}-3,3-dimethyl-2-p-toluenesulfonylguanidine was obtained by recrystallization from isopropyl alcohol, m.p. 168 - 70°, yield 28%. Analysis, calculated for $C_{19}H_{24}N_4O_2S$: C, 61.27; H, 6.49; N, 15.04; S, 8.61; found: C, 61.40; H, 6.35; N, 15.26; S, 8.41.

(e) 2,4,6-Tris(dimethylamino)-1,3,5-triazine from dimethylcyanamide and phenyllithium in benzene, hexane.

The procedure was the same as that of the general method previously described in section (a) except that dry benzene was used instead of absolute ethyl ether. Phenyllithium (0.05 mole) was prepared in a solution of equal volumes of dry benzene and absolute ether and most of the ether was distilled out before addition of the solution of dimethylcyanamide (0.10 mole) in dry benzene. The major product was 2,4,6-tris(dimethylamino)-1,3,5-triazine, yield 53% and the minor product was 2,4-bis(dimethylamino)-6-phenyl-1,3,5-triazine, yield 1%. When dry hexane was used as solvent, the yield of 2,4,6-tris(dimethylamino)-1,3,5-triazine was 56% and 2,6-bis(dimethylamino)-6-phenyl-1,3,5-triazine was present just as an impurity.

(f) 2,4,6-Tris(dimethylamino)-1,3,5-triazine from lithium dimethylamide and dimethylcyanamide.

A solution of 2.55 g. (0.05 mole) of lithium dimethylamide in 100 ml. of absolute ether was prepared by the use of Cope's method (25), except that the reaction vessel was kept in a "Dry Ice" acetone cooling bath.

The cooling bath was removed and a solution of 14 g. (0.20 mole) of dimethylcyanamide in 20 ml. of absolute ether was added to the reaction vessel at a rate that maintained the solution at reflux. After the addition was completed, the solution was refluxed for 30 minutes. The solution was then cooled in an ice-bath and an equal volume of cold water was added slowly. After stirring for another 5 minutes, the two layers were separated. The aqueous layer was extracted twice with an equal volume of ether and the combined ether extract was washed with cold water then dried over anhydrous magnesium sulfate. The solvent was removed by distillation. After recrystallization from 95% ethanol, needle-shaped crystals of 2,4,6-tris(dimethylamino)-1,3,5-triazine were obtained, yield 8%, m.p. 169 - 70^0. Most of the cyanamide was recovered.

After standing overnight, no crystals were obtained from the aqueous layer.

(g) <u>2,4-Bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine and 2,4,6-tris(1-pyrrolidinyl)-1,3,5-triazine.</u>

The procedure of this experiment was exactly the same as that of the general method previously described in section (a) except that N-cyanopyrrolidine was used instead of dimethylcyanamide and that the ratio of N-cyanopyrrolidine to phenyllithium was 2.5 : 1.

During the addition of cold water to the ethereal solution, a white precipitate was observed at the interface of the two layers. This compound was collected, washed several times with cold water and recrystallized from dimethoxyethane. It was identified as 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine and combined with material obtained below. Analysis, calculated for $C_{17}H_{21}N_5$: C, 69.12; H, 7.17; N, 23.71; found: C, 69.30; H, 7.64; N, 23.06.

The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ether extract was dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the unreacted materials were distilled under reduced pressure. The residue in the distilling flask was collected and recrystallized from dimethoxyethane. Thin layer chromatography on silica gel showed that it was a mixture of 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine and 2,4,6-tris(1-pyrrolidinyl)-1,3,5-triazine. These two compounds could be separated by passing through a silica gel column, eluting with a solution of one part of acetone in fifteen parts of chloroform. The total yield of 2,4-bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine was 41%. The symmetrical triazine was present as an impurity. After recrystallization from dimethoxyethane containing a small amount of water, colourless crystals of 2,4,6-tris(1-pyrrolidinyl)-1,3,5-triazine were obtained, m.p. 184.5 - 7°, literature m.p. 186.6 - 9.8° (26). Analysis, calculated for $C_{15}H_{24}N_6$: C, 62.47; H, 8.39; N, 29.14; found: C, 62.29; H, 8,45; N, 29.18.

After standing overnight, no crystals were obtained from the aqueous layer.

(h) 1,1-Tetramethylene-2-benzoylguanidine

The procedure was the same as that of the general method previously described in section (a) except for the steps described below and that the ratio of N-cyanopyrrolidine to phenyllithium was 3 : 2.

After separation of the two layers, the aqueous layer was allowed to stand overnight and needle-shaped crystals of 1,1-tetramethylene-2-benzoylguanidine were collected, washed several times with cold water and recrystallized from benzene, yield 12%, m.p. 167 - 8°. Analysis, calculated for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34; found: C, 66.21; H, 6.89; N, 19.51.

2,4-Bis(1-pyrrolidinyl)-6-phenyl-1,3,5-triazine was obtained from the ethereal layer, yield 22%.

(i) N,N-Tetramethylenebenzamidine and N,N-tetramethylene-N'-p-toluenesulfonylbenzamidine.

The procedure of this experiment was the same as that previously described in section (a) except that the ratio of N-cyanopyrrolidine to phenyllithium was 1 : 1.

After addition of cold water to the ether solution, the two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. The combined ether extract was dried over anhydrous magnesium sulfate. After distillation of ether, 3.12 g. (25%) of crude N,N-tetramethylenebenzamidine was obtained.

The crude N,N-tetramethylenebenzamidine (3.12 g., 0.017 mole) was dissolved in 16 ml. acetone and transferred to a 50 ml. conical flask containing 1.6 g. of 50% sodium hydroxide solution. A solution of 3.8 g. (0.02 mole) of p-toluenesulfonyl chloride in minimum of acetone was added slowly to the conical flask with stirring and cooling. A brown colour developed immediately. After stirring for 20 minutes, 80 ml. of ice-cold water was added to the reaction mixture then it was stirred for another 30 minutes. Crystals of N,N-tetramethylene-N'-*p*-toluenesulfonylbenzamidine were collected, washed several times with cold water and recrystallized from ethyl acetate, m.p. 150 - 1°, yield 39%. Analysis, calculated for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53; S, 9.75; found: C, 65.92; H, 6.00; N, 8.37; S, 9.60.

When the ratio of phenyllithium to N-cyanopyrrolidine was 2 : 1, the sole product, N,N-tetramethylenebenzamidine, was obtained in 24% yield.

(j) 1-{α-(1-Pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine and 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethylene-2-p-toluenesulfonylguanidine.

Instead of standing overnight, the aqueous layer from section (i) was extracted immediately with an equal volume of chloroform. The chloroform extract was washed with cold water and dried over anhydrous magnesium sulfate. After removal of the solvent, crude 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine was obtained, yield 4.17 g. (38%).

1-{α-(1-Pyrrolidinyl)benzylidene}-3,3-tetramethylene-2-*p*-toluenesulfonylguanidine was prepared by the same method as was used for preparation of N,N-tetramethylene-N'-*p*-toluenesulfonylbenzamidine. The quantities of chemicals used were: 1-{α-(1-pyrrolidinyl)benzylidene}-3,3-tetramethyleneguanidine, 4.17 g. (0.015 mole); 50% sodium hydroxide solution, 1.6 g. (0.02 mole); p-toluenesulfonyl chloride, 3.6 g. (0.019 mole). The product was obtained as colourless crystals from methanol, m.p. 221 - 3^0 (decomposed), yield 28%. Analysis, calculated for $C_{23}H_{28}N_4O_2S$: C, 65.07; H, 6.65; N, 13.20; S, 7.55; found: C, 65.03; H, 6.52; N, 13.25; S, 7.45.

(k) 1,3-Dimethyl-1,3-diphenyl-2-cyanoguanidine

The procedure of the first part of this experiment was the same as that of the method of Lettré (9). When the addition of a solution of 8.4 g. (0.1 mole) of phenyllithium in 100 ml. absolute ether to the solution of 32.5 g. (0.24 mole) of N-methyl-N-cyanoaniline in 35 ml. of absolute ether was completed, the reaction mixture was refluxed for 30 minutes. A white precipitate was observed. An equal volume of cold water was added slowly to the flask and the two layers were stirred for another 10 minutes. The white precipitates at the interface of the two layers were collected, washed several times with cold water and recrystallized from carbon tetrachloride. This compound was identified as 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine, m.p. 126 - 126.5^0. Analysis, calculated for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20; found: C, 72.60; H, 6.08; N, 21.30. The two layers were separated and the aqueous layer was extracted twice with an equal volume of ether. Then, the combined ether extract was washed twice with dilute hydrochloric acid solution, water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation and benzonitrile and unreacted materials were collected at reduced pressure. A pure sample of benzonitrile was obtained by passing the mixture through an alumina column (neutral), eluting with a solution of 5 parts of petroleum ether (60 - 80^0) in 3 parts of benzene, yield 4%. A second crop of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine was obtained by recrystallization of the residue in the distilling flask from carbon tetrachloride, total yield 57%.

(l) <u>1,3-Dimethyl-1,3-diphenylguanidine and its salts.</u>

The dilute hydrochloric acid wash solution from section (k) was allowed to stand overnight, but no precipitate was obtained. It was cooled in an ice-bath with stirring and neutralized with 6<u>N</u> sodium hydroxide solution then was made strongly basic by adding 5 ml. in excess. The basic solution was extracted twice with an equal volume of ether and the combined ether extract was washed with water then dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the thick liquid, which was identified as 1,3-dimethyl-1,3-diphenylguanidine, was collected at 105 - 10^0 at 0.05 mm. pressure, R. L. Meek <u>et</u> <u>al</u> (15) reported b.p. 124^0 at 0.07 mm. pressure or 134^0 at 0.5 mm. pressure, yield 7%. The infrared spectrum of this compound was identical with that obtained by R. L. Meek <u>et</u> <u>al</u>.

A white precipitate of the hydrochloride of 1,3-dimethyl-1,3-diphenylguanidine was obtained by passing hydrogen chloride gas into a solution of 0.875 g. (0.0037 mole) of this guanidine in 15 ml. of dry ether. The crude product was dissolved in a minimum amount of cold methanol and reprecipitated by slow addition of dry ether with swirling. The compound sintered at 238^0 (colour turned blue) and melted rapidly at 242 - 243^0 with decomposition, literature m.p. 238^0 (15), yield 60%. The salt from hydrogen bromide was prepared by the same method. It also sintered at 237^0 and melted rapidly at 243 - 244^0 with decomposition, literature m.p. 244 - 5^0 (15), yield 88%.

(m) <u>1,3-Dimethyl-1,3-diphenyl-2-cyanoguanidine from N-methyl-N-cyanoaniline and lithium methylphenylamide.</u>

Lithium methylphenylamide was prepared as follows. A solution of 16 g. (0.15 mole) of N-methylaniline in 20 ml. absolute ether was added slowly to a solution of 0.1 mole of phenyllithium in 60 ml. absolute ether at such a rate that it maintained the solution at reflux. After the completion of addition, the solution was heated under reflux for 30 minutes.

The procedure of the other parts of this experiment was the same as that previously described in section (k) except that a solution of 26.4 g. (0.2 mole) of N-methyl-N-cyanoaniline in 20 ml. of absolute ether was added to the solution of lithium methylphenylamide.

When the addition of solution of N-methyl-N-cyanoaniline was completed, the reaction mixture was refluxed for 30 minutes. The white precipitate of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine was filtered. A second crop was obtained from the ether layer, total yield 85%. No benzonitrile was obtained from the ethereal layer.

(n) Hydrolysis of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine

A mixture of 2.0 g. (0.0076 mole) of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine and 60 ml. of 6N hydrochloric acid solution was heated gently until the solution was clear. It was cooled in an ice-bath and neutralized with 6N sodium hydroxide. A white precipitate of 1,3-dimethyl-1,3-diphenyl-2-carbamylguanidine was collected, washed, dried and recrystallized from pyridine, m.p. 154 - 5^0, yield 80%. Analysis, calculated for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85; found: C, 68.19; H, 6.39; N, 20.01.

A mixture of 4 g. (0.015 mole) of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine and 100 ml. of 6N hydrochloric acid solution was refluxed for 24 hours. The acidic solution was cooled and made strongly basic by slow addition of excess 6N sodium hydroxide solution. The basic solution was extracted twice with an equal volume of ether and the combined ether extract was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed by distillation and the thick liquid of 1,3-dimethyl-1,3-diphenylguanidine was collected at 105 - 110^0 at 0.05 mm. pressure, yield 86%.

A mixture of 1,3-dimethyl-1,3-diphenyl-2-cyanoguanidine and 3N sodium hydroxide solution was refluxed for 48 hours. The solution was cooled to room temperature and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and distilled. A pure sample,N,N'-dimethyl-N,N'-diphenyl-urea, was obtained by recrystallization from ether, m.p. 118 - 9°, literature m.p. 121° (27). This compound was shown by mixture melting point and infrared spectrum to be identical with a authentic specimen obtained by the method of Michler (28).

(o) Action of phenyllithium on diphenylcyanamide

The procedure and the relative amount of diphenylcyanamide and phenyllithium used were the same as that previously described in section (k). In this experiment, benzonitrile was the only product isolated, yield 10%.

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